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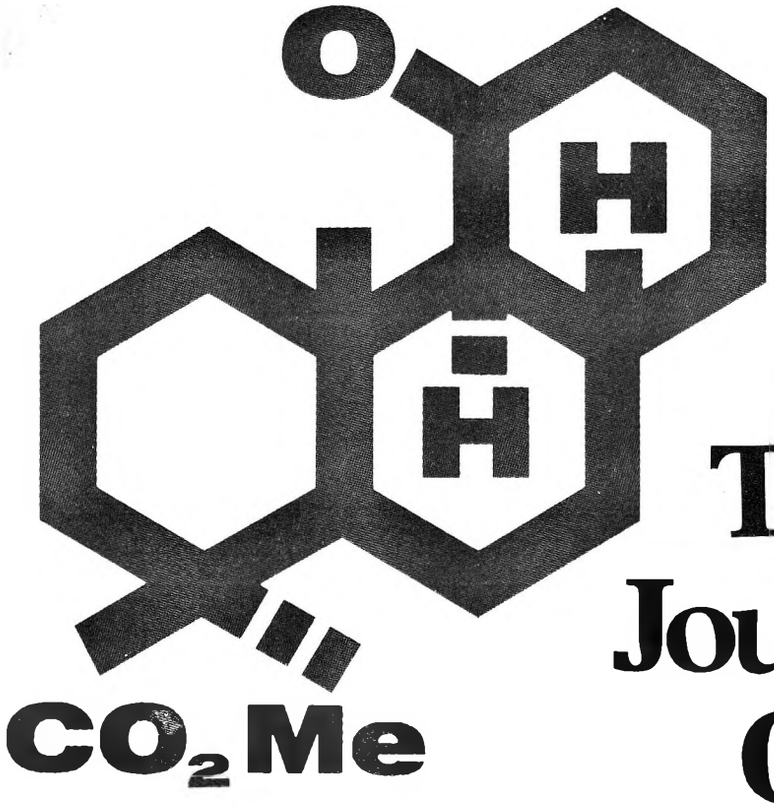

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Stereoselective Syntheses of ((*E*)- and (*Z*)-1-Halo-1-alkenyl)silanes from Alkynes

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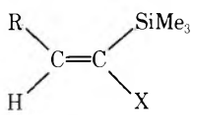
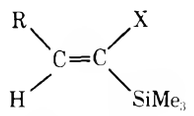
Received December 19, 1977

((*E*)-1-Haloalkenyl)trimethylsilanes are produced in high isomeric purities and yields by *N*-chlorosuccinimide, bromine, or iodine treatment of the monohydroalumination products derived from the reaction of (1-alkynyl)trimethylsilanes and diisobutylaluminum hydride in ether solvent. The corresponding ((*Z*)-1-chloro- and (*Z*)-1-bromoalkenyl)silanes may be obtained through bromine-catalyzed isomerization of the ((*E*)-1-chloro- and (*E*)-1-bromoalkenyl)silanes. Both (*E*)- and (*Z*)-1-haloalkenyl)silanes undergo metal–halogen exchange when treated with butyllithium to give ((*Z*)- and (*E*)-1-lithioalkenyl)silanes, respectively.

(α-Halovinyl)silanes ($H_2C{=}CXSiR_3$) are exceedingly versatile synthetic intermediates for use in a variety of chemical transformations,[1] and convenient procedures[2] for their synthesis are available. However, published procedures for preparation of the potentially valuable β-alkyl-substituted ((*E*)- and (*Z*)-1-halo-1-alkenyl)silanes are lacking. In connection with ongoing synthetic work, our need for ready access to these intermediates prompted us to explore their syntheses from 1-alkynes via conversion into (α-silylalkenyl)alanes.[3] Since we have previously shown that treatment of alkenylalanes with *N*-chlorosuccinimide,[4] bromine,[5] or iodine[5] results in preferential cleavage of the vinyl carbon–aluminum bond to afford the corresponding isomerically pure vinyl halides, it was hoped that halogenation of (α-silylalkenyl)alanes might provide the desired (α-haloalkenyl)silanes. Our investigations into these possibilities have uncovered operationally convenient stereoselective syntheses for ((*E*)- and (*Z*)-α-haloalkenyl)silanes **1** and **2**.



1(a–d)–X
X = Cl, Br, I

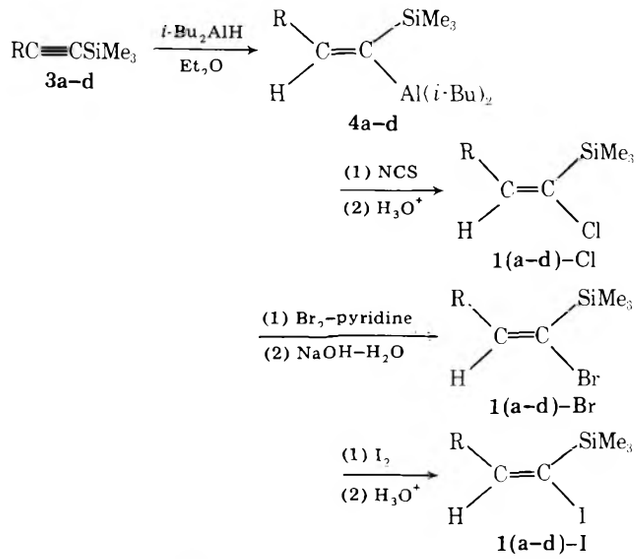


2(a–d)–X
X = Cl, Br

a, R = *n*-butyl; **b**, R = cyclohexyl; **c**, R = *tert*-butyl; **d**, R = cyclohexenyl

Results and Discussion

((*E*)-1-Halo-1-alkenyl)silanes. The hydroalumination of (1-alkynyl)silanes **3** with diisobutylaluminum hydride in ether solvent[6–8] proceeds in a stereo- and regiospecific manner to produce ((*Z*)-1-alumino-1-alkenyl)silanes **4** regardless of the steric requirements of the alkyl group at the β carbon of the (1-alkynyl)silanes. Attempts to chlorinate **4** with chlorine



3a–d → (*i*-Bu$_2$AlH, Et$_2$O) → **4a–d**

4a–d → (1) NCS, (2) H_3O^+ → **1(a–d)–Cl**

4a–d → (1) Br_2–pyridine, (2) NaOH–H_2O → **1(a–d)–Br**

4a–d → (1) I_2, (2) H_3O^+ → **1(a–d)–I**

a, R = *n*-butyl; **b**, R = cyclohexyl; **c**, R = *tert*-butyl; **d**, R = cyclohexenyl

in methylene chloride at −78 °C resulted in low yields of the desired (α-chloroalkenyl)silane **1**–Cl. Fortunately, however, this difficulty could be obviated by the use of *N*-chlorosuccinimide (NCS) as the chlorinating agent. Thus, the silylacetylene **3** was treated with diisobutylaluminum hydride (1.0 equiv) in ether solvent and heated at 40 °C for 1 h. To the resultant ((*Z*)-1-alumino-1-alkenyl)silane **4**, NCS (1.1 equiv) was added in the dark with cooling to maintain the temperature between −25 and −20 °C. Stirring the reaction mixture for an additional 30 min at 0 °C followed by a hydrolytic workup afforded the ((*E*)-1-chloro-1-alkenyl)silanes **1**–Cl in greater than 80% yields (Table I).

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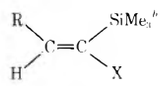
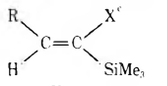
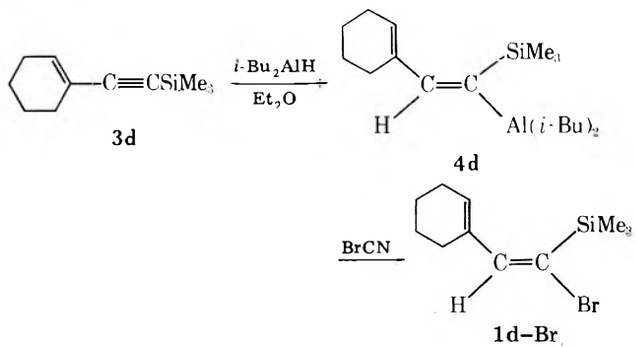
Table I. Isolated Yields of ((*E*)- and (*Z*)-1-Halo-1-alkenyl)trimethylsilanes Derived from (1-Alkynyl)trimethylsilanes[a]

RC≡CSiMe$_3$, R=	Registry no.	 X=	Registry no.	 X=	Registry no.
n-Butyl	3844-94-8	Cl (84)	66270-61-9	Cl (81)[d]	66270-69-7
		Br (90)	66270-62-0	Br (81)[d]	66270-70-0
		I (90)	66270-63-1		
Cyclohexyl	66270-60-8	Cl (87)	66270-64-2	Cl (91)[d]	66270-71-1
		Br (96)	66270-65-3	Br (92)[d]	66270-72-2
				Br (89)[e]	
		I (90)	66270-66-4		
tert-Butyl	14630-42-3	Br (86)	65425-93-6	Br (89)[e]	65425-94-7
				Br (88)[f]	
		I (85)	66270-67-5		
Cyclohexenyl	17988-44-2	Br (84)	66270-68-6	Br (84)[f]	66270-73-3

[a] All compounds were at least 97% isomerically pure by GLC analysis on a 55-m OV-101 or SE-30 glass capillary column; % yields are in parentheses. [b] Via hydroalumination–halogenation. [c] Via hydroalumination–halogenation–isomerization. [d] Isomerization of crude *E* isomer in ether with bromine–pyridine while irradiating with a UV lamp. [e] Isomerization of quenched reaction mixture containing the *E* isomer with bromine in ambient light. [f] Via trans hydroalumination–bromination.

The synthesis of ((*E*)-1-bromo-1-alkenyl)silanes **1(a–c)–Br** required addition of bromine (1.3 equiv) in methylene chloride to a solution of **4** at low temperature in ether containing pyridine (2 equiv). This was followed by hydrolysis of the reaction mixture in cold dilute sodium hydroxide. A 30% excess of bromine was employed to compensate for some isobutyl group cleavage from the diisobutylalanyl moiety. The presence of pyridine in the bromination step represses addition of bromine to the double bond of **4** and/or **1–Br** and results in higher yields of the desired (α-bromoalkenyl)silanes (Table I). Quenching of the bromination mixture was done in an aqueous solution of sodium hydroxide rather than in dilute hydrochloric acid because the latter procedure caused partial isomerization of the double bond.

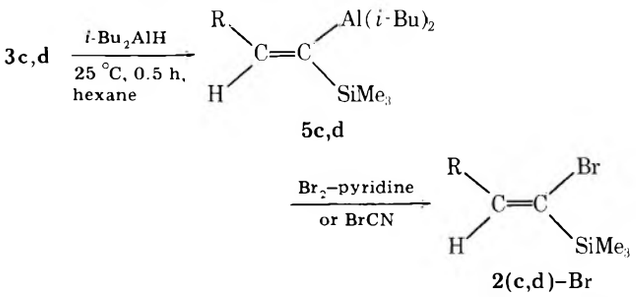
Extension of the bromination reaction to (dienylsilyl)alane **4d**, accessible through the chemo- and regioselective hydroalumination of (2-cyclohexenylethynyl)trimethylsilane (**3d**), produced a mixture of products. This probably was the result of a competition for bromine between the carbon–carbon double bonds and the vinyl carbon–aluminum bond of **4d**. However, **4d** was successfully converted into the desired bromide **1d–Br** by treatment with a predried solution of cyanogen bromide.



3d **4d** **1d–Br**

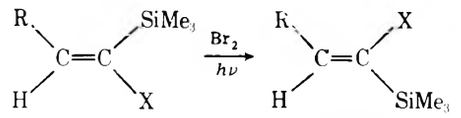
Finally, treatment of **4a–c** in ether solvent with iodine (1.3 equiv) furnished, after quenching the reaction mixture in dilute hydrochloric acid, the anticipated ((*E*)-1-iodo-1-alkenyl)silanes **1(a–c)–I** in better than 80% yields. A summary of the yields of ((*E*)-1-halo-1-alkenyl)silanes obtained using our procedures is presented in Table I.

((*Z*)-1-Halo-1-alkenyl)silanes. Having developed convenient syntheses for the ((*E*)-1-halo-1-alkenyl)silanes, we next turned our attention to finding routes to the corresponding *Z* halides. An obvious method for achieving this goal appeared to be through the halogenation of ((*E*)-1-alumino-1-alkenyl)silanes **5**. It has been shown that these are accessible through hydroalumination of (3,3-dimethyl-1-butynyl)trimethylsilane (**3c**) or (2-methylbut-1-en-3-yn-4-yl)trimethylsilane in hydrocarbon solvent.[3]



As expected, bromination of **5c** in the presence of pyridine indeed afforded the anticipated ((*Z*)-1-bromo-1-alkenyl)silane **2c–Br** containing only 1% of the *E* isomer. Also, treatment of enynylsilane **3d** with diisobutylaluminum hydride followed by addition of a solution of cyanogen bromide in methylene chloride yielded, after workup, the (*Z*)-dienylsilyl bromide **2d–Br**. Unfortunately, however, this approach to ((*Z*)-1-halo-1-alkenyl)silanes did not turn out to be general because hydroalumination of (1-alkynyl)trimethylsilanes containing primary or secondary β-alkyl substituents yielded mixtures of ((*Z*)- and (*E*)-1-alumino-1-alkenyl)silanes along with dihydroaluminated product. For example, when (1-hexynyl)-trimethylsilane (**3a**) was treated with diisobutylaluminum hydride (1.1 equiv) in heptane solvent at 25 °C for 16 h followed by hydrolysis with dilute hydrochloric acid, GLC analysis of the products on a SE-30 glass capillary column (55 m) revealed (*cis*-1-hexenyl)trimethylsilane (11%), (*trans*-1-hexenyl)trimethylsilane (34%), and (*n*-hexyl)trimethylsilane (27%).[9,10]

Fortunately, a general method for preparing ((*Z*)-1-bromo-1-alkenyl)silanes **2–Br** emerged when it was discovered that bromine in the presence of light catalyzes isomerization of the *E* bromides **1–Br** into the desired *Z* isomers **2–Br**. Thus, after hydrolysis of the bromination mixture containing **1b–Br** or **1c–Br** with dilute hydrochloric acid, 10 mol % of bromine was added in two equal portions at the beginning and middle of a 60-min period while exposing the two-phase mixtures to ambient light and stirring vigorously at 25 °C. Then they were treated with aqueous sodium sulfite to decompose the excess bromine. Extraction with pentane and distillation afforded the ((*Z*)-1-bromo-1-alkenyl)silanes **2b–Br** and **2c–Br** in at least 97% isomeric purities.

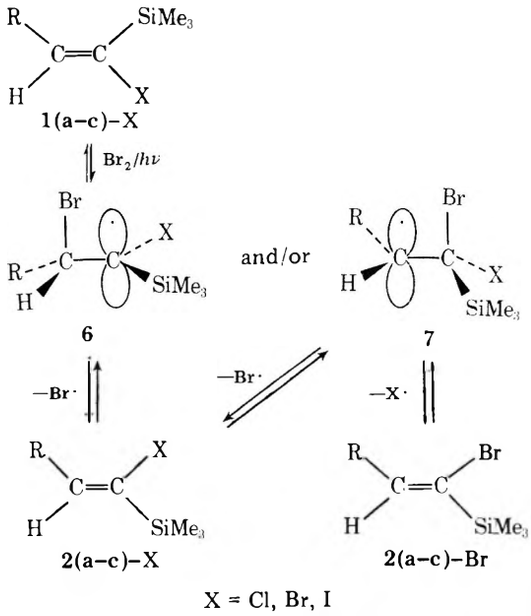


1(a–c)–Cl 2(a–c)–Cl
1(a–c)–Br 2(a–c)–Br

This operationally simple procedure, which does not require prior isolation of the *E* bromide precursors **1**–Br, is very effective and proceeds rapidly when applied to alkynylsilanes containing secondary or tertiary alkyl groups. However, it was noted that under the above conditions isomerization of **1a**–Br, containing a primary alkyl group, proceeded much more slowly. This may result from a relatively fast, irreversible reaction of bromine with the substrate. However, this difficulty was obviated by slight modification of the experimental procedure. Thus, after hydrolysis with dilute hydrochloric acid, the *E* bromide **1a**–Br was extracted into ether, and the combined extract was washed successively with dilute hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. After drying over magnesium sulfate and filtration, the etheral solution containing **1a**–Br was treated at room temperature with pyridine (6 equiv based on Br_2) and with 15 mol % of bromine in methylene chloride in three equal portions after 0, 30, and 60 min during a 90-min period while irradiating with a UV sunlamp (275 W). After workup and distillation, there was obtained an 81% yield of **2a**–Br containing only 3% of the *E* isomer **1a**–Br.

The above isomerization procedures were also very effective for the conversion of ((*E*)-1-chloro-1-alkenyl)silanes to the corresponding *Z* isomers (Table I). However, attempts to isomerize ((*E*)-1-iodo-1-alkenyl)silanes in the presence of bromine–pyridine while irradiating the mixture with a sunlamp resulted in appreciable exchange of iodine by bromine. A summary of the yields of ((*Z*)-1-chloro- and (*Z*)-1-bromo-1-alkenyl)silanes obtained via the bromine-catalyzed isomerizations is shown in Table I.

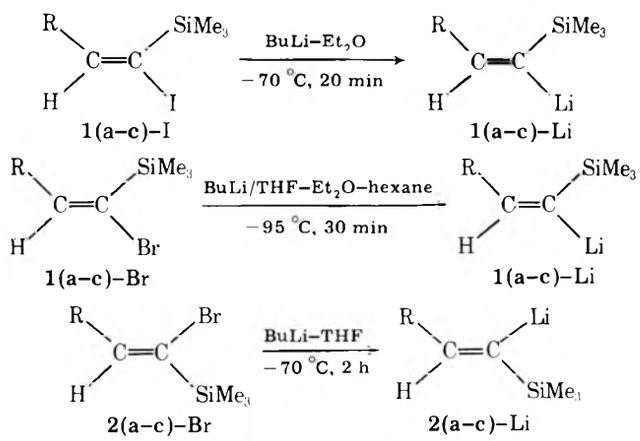
The isomerization of ((*E*)-1-halo-1-alkenyl)silanes (**1** → **2**) is reminiscent of the bromine-catalyzed cis–trans isomerization of 1,2-dibromoethylene, which has been subjected to a detailed mechanistic study.[11] Thus, addition of bromine atoms resulting from photolytic dissociation of Br_2 to 1–X produces the radicals **6** and/or **7**, depicted in their most stable conformations. Since both a trialkylsilyl moiety[12] and a halogen[13] are known to stabilize an adjacent radical center, formation of radical **6** should be favored over that of **7**. When X = Br, loss of a bromine from either **6** or **7** leads to the observed sterically less hindered *Z* bromides **2**–Br. However, when X represents either Cl or I in radical **7**, these halogen atoms may be lost competitively with the bromine atom, thus producing mixtures of products containing both **2**–Br and **2**–Cl or **2**–I, respectively. The fact that the bond dissociation energy of the C–Cl bond is larger than that of the C–Br bond suggests the preferential ejection of the bromine atom. In agreement with this is the observation that bromine-catalyzed isomerizations of ((*E*)-1-chloro-1-alkenyl)silanes **1**–Cl afford the corresponding *Z* isomers **2**–Cl in high isomeric purities and essentially free of the corresponding bromides **2**–Br. A different situation exists when X in **7** is iodine. In this case, loss of the iodine atom from radical **7** (X = I) should be favored over dissociation of the bromine atom. This was born out by the fact that attempted isomerization of **1a**–I afforded, besides the *Z* iodide **2a**–I, a mixture of the corresponding *Z* bromide **2a**–Br and the thermodynamically less favored *E* bromide **1a**–Br.



X = Cl, Br, I

((*E*)- and (*Z*)-1-Lithio-1-alkenyl)silanes. Having both ((*E*)- and (*Z*)-1-halo-1-alkenyl)silanes readily available, we finally directed our efforts to their conversion into the corresponding (α-lithioalkenyl)silanes. This reaction is of considerable interest not only in connection with synthetic methodology, but it also provides a convenient tool for establishing the stereochemistries of the (α-haloalkenyl)silanes obtained in the present study.

Previous attempts to prepare (α-lithioalkenyl)silanes by metalation of (*cis*- and *trans*-alkenyl)silanes have resulted in isomeric mixtures of products and/or competing metalation of the trimethylsilyl moiety.[14] On the other hand, we have now found that metal–halogen exchange of the ((*E*)- and (*Z*)-1-bromo- or (*E*)-1-iodoalkenyl)silanes with butyllithium provides efficient, stereoselective syntheses for ((*E*)- and (*Z*)-1-lithioalkenyl)silanes.[15] Thus, addition of butyllithium (1.1 equiv) in hexane to a solution of ((*E*)-1-iodoalkenyl)silanes **1(a–c)**–I in ether at −70 °C produces the corresponding



((*Z*)-1-lithioalkenyl)silanes **1(a–c)**–Li in better than 90% yields and containing less than 7% of the trans isomers. This was evidenced by the stereochemistries of the vinyl silanes formed on protonolysis of the intermediate (α-lithioalkenyl)-silanes with methanol (Table II). For metal–halogen exchange involving *E* bromides **1(a–c)**–Br, the presence of tetrahydrofuran was required. To repress coupling of the product **1**–Li with the accompanying butyl bromide,[16,17] the reaction had to be carried out at −95 °C for 30 min using a mixture of tetrahydrofuran–ether–*n*-hexane.[18]

Exchange of the sterically more hindered bromide in ((*Z*)-1-bromo-1-alkenyl)silanes **2(a–c)**–Br by butyllithium occurred more slowly and had to be carried out at −70 °C for 2 h. With either isomer, however, nearly quantitative conversions into the lithio compounds **1**–Li and **2**–Li with retention of stereochemistry were achieved (Table II).

Table II. Lithiation–Protonation of ((*E*)- and (*Z*)-1-Halo-1-alkenyl)trimethylsilanes

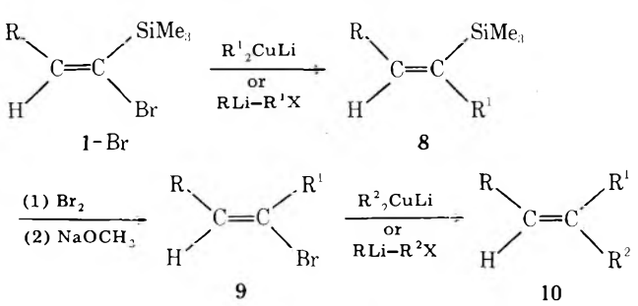
(1-Halo-1-alkenyl)silane	Lithiation[a]			Alkenylsilane[b]	GLC yield of alkenylsilanes,[c] %
	Solvent	Temp, °C	Time, min	Cis:trans	
1a–Br	Trapp[d]	−95	30	99:1[e]	88
1b–Br	Trapp	−95	30	99:1[f]	92
1c–Br	Trapp	−95	30	90:10[g]	89
2a–Br	THF	−70	120	1:99	96
2b–Br	THF	−70	120	1:99	96
2c–Br	THF	−70	120	1:99	99
1a–I	Et_2O	−70	20	93:7	93
1b–I	Et_2O	−70	20	98:2	98
1c–I	Et_2O	−70	20	96:4	99

[a] By treatment with *n*-butyllithium (1.1 equiv) under the specified conditions. [b] After quenching of the (1-lithio-1-alkenyl)silanes with excess methanol. Isomeric purities were determined by GLC comparison with authentic samples. [c] The GLC chromatogram also revealed peaks with retention times corresponding to the starting material and to the coupling product derived from the (1-lithio-1-alkenyl)silane with butyl bromide. [d] Mixture of THF–Et_2O–*n*-hexane (4:1:1). [e] Registry no.: cis, 54731-58-7; trans, 66270-75-5. [f] Registry no.: cis, 52835-06-0; trans, 20107-37-3. [g] Registry no.: cis, 66270-74-4; trans, 26567-95-3.

Finally, attempted metal–halogen exchange on the (α-chloroalkenyl)silane **1a**–Cl using *n*-butyl- or *sec*-butyllithium did not furnish the anticipated (*cis*-1-hexenyl)trimethylsilane after hydrolysis, but afforded a mixture of products containing starting material, (1-hexynyl)trimethylsilane, and several unidentified compounds. Conclusive proof of the stereochemistries of both the ((*E*)- and (*Z*)-1-chloro-1-hexenyl)trimethylsilanes **1a**–Cl and **2a**–Cl was obtained by their conversion into (*Z*)- and (*E*)-2-trimethylsilyl-2-heptenes via alkylation with methyllithium in the presence of a catalytic amount of cuprous iodide.[19,20]

Summary

Operationally simple syntheses of ((*E*)- and (*Z*)-1-halo-1-alkenyl)silanes are described. The precursors are readily available via the regio- and stereoselective monohydroalumination of (1-alkynyl)trimethylsilanes. Treatment of the resultant ((*Z*)-1-alumino-1-alkenyl)silanes with NCS, bromine, or iodine produces the corresponding ((*E*)-1-halo-1-alkenyl)silanes in high yields and isomeric purities. Bromine-catalyzed isomerization of ((*E*)-1-chloro- and (*E*)-1-bromo-1-alkenyl)silanes affords the corresponding *Z* isomers. As exemplified below, these (α-haloalkenyl)silanes provide a valuable entry to stereoselective synthesis of dialkyl-substituted (vinyl)silanes (**8**),[19] alkenyl halides (**9**),[19,21] and trisubstituted olefins (**10**).[19] The corresponding compounds with opposite stereochemistries are available using the ((*Z*)-1-bromo-1-alkenyl)silanes.[19]



Experimental Section

All boiling points are uncorrected. Infrared spectra were obtained on a Beckman IR-8 spectrometer. ^1H NMR spectra were recorded on a Varian A-60 spectrometer, and chemical shifts are reported in ppm downfield from a Me_4Si internal standard. High-resolution mass measurements were obtained on a DuPont 21-492B mass spectrometer. GLC analyses were performed on a Varian 600-D gas chromatograph equipped with 5-ft columns packed with 20% dodecamethylenedinitrile, didecyl phthalate, or SF-96 on Gas-Chrome R, Q, or Q, respectively, or on a Varian 1400 gas chromatograph equipped with either a 55-m OV-101 or SE-30 glass capillary column.

The hydrocarbons (Phillips) and anhydrous diethyl ether (Mallinckrodt) were used as received. NCS (Aldrich) was recrystallized from methylene chloride and dried over phosphorus pentoxide. All alkynes employed in the study were purchased from Farchan and were used after checking their ^1H NMR spectra, indices of refraction, and GLC retention times. The concentration of butyllithium (Ventron or Aldrich) in *n*-hexane was determined by titration using 2,2′-biquinoline as an indicator.[22] Diisobutylaluminum hydride (Texas Alkyls) was transferred from the lecture bottle into a storage flask which was maintained under an N_2 atmosphere. The neat reagent (5.4 M) was transferred by means of a syringe.

All glassware for reactions involving organoaluminum or organolithium reagents was oven-dried at 150 °C for 6 h, assembled hot, and cooled under a stream of purified nitrogen before use. All reactions involving these materials were stirred magnetically and carried out under an atmosphere of nitrogen.

General Procedure for the Preparation of (1-Alkynyl)trimethylsilanes. (1-Hexynyl)trimethylsilane (3a). A solution of 1-hexyne (24.7 g, 0.300 mol) in 100 mL of anhydrous ether was treated consecutively at −70 °C with a solution of butyllithium (0.306 mol) in *n*-hexane and with trimethylchlorosilane (33.2 g, 0.306 mol). The reaction mixture was allowed to exotherm to room temperature, where it was stirred for 2 h and then quenched in ice water. The layers were separated, and the aqueous layer was extracted with *n*-pentane. The combined pentane extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Distillation of the residue gave 41.2 g (89%) of **3a:** bp 71–73 °C (36 Torr); $n^{23}D$ 1.4305 (lit.[23] bp 155 °C, $n^{20}D$ 1.4318); IR (neat) 2185, 1251, and 843 cm^{-1}; NMR (CCl_4) δ 2.3–0.9 (m, 9 H) and 0.11 (s, 9 H).

(2-Cyclohexylethynyl)trimethylsilane (3b). Following the general procedure described above, cyclohexylacetylene was converted to **3b** in 86% yield: bp 82–83 °C (7 Torr); $n^{22}D$ 1.4615; IR (neat) 2185, 1250, and 845 cm^{-1}; NMR (CCl_4) δ 2.5–1.0 (m, 11 H) and 0.12 (s, 9 H); exact mass, *m/e* 180.1340 (calcd for $C_{11}H_{20}Si$, 180.1335).

(3,3-Dimethyl-1-butynyl)trimethylsilane (3c). Following the general procedure, *tert*-butylacetylene was converted to **3c** in 82% yield: bp 80–81 °C (150 Torr); $n^{23}D$ 1.4161 (lit.[24] bp 57 °C (60 Torr), $n^{20}D$ 1.4161); IR (neat) 2165, 1252, and 842 cm^{-1}; NMR (CCl_4) δ 1.22 (s, 9 H) and 0.11 (s, 9 H).

(2-Cyclohexenylethynyl)trimethylsilane (3d). Following the general procedure described previously, 1-ethynylcyclohexene was converted to **3d** in 89% yield: bp 55–57 °C (1 Torr); $n^{23}D$ 1.4915 (lit.[25] bp 107–108 °C (20 Torr), $n^{20}D$ 1.4940); IR (neat) 2160, 1250, 870, and 845 cm^{-1}; NMR (CCl_4) δ 6.07 (m, 1 H), 2.05 (m, 4 H), 1.60 (m, 4 H), and 0.14 (s, 9 H).

General Procedure for the Preparation of ((*E*)-1-Chloro-1-alkenyl)trimethylsilanes. ((*E*)-1-Chloro-1-hexenyl)trimethylsilane (1a–Cl). Into a dry 25-mL three-neck round-bottom flask equipped with a nitrogen inlet and thermometer and kept under a static pressure of nitrogen was added **3a** (1.54 g, 10 mmol) and anhydrous ether (5 mL). Diisobutylaluminum hydride (1.85 mL, 10 mmol) was added dropwise using a syringe while maintaining the temperature during the addition at 25–30 °C by means of a water bath. The solution was stirred at room temperature for 15 min and then heated at 40 °C for 1 h. After cooling to −25 °C (aqueous $CaCl_2$–dry ice bath[26]) and diluting with anhydrous ether (5 mL), the

reaction mixture was treated in the dark with dry solid *N*-chlorosuccinimide (1.47 g, 11 mmol) at such a rate as to maintain the temperature below −20 °C. After completion of the NCS addition, the reaction mixture was stirred in the dark for an additional 15 min at −25 °C and then for 30 min at 0 °C. The resultant yellowish solution was slowly poured into chilled, stirred 10% hydrochloric acid (50 mL). Stirring was continued until the resulting phases became clear. The layers were separated, the water layer was extracted with *n*-pentane, and the combined organic extracts were washed with 10% hydrochloric acid followed by saturated aqueous sodium bicarbonate. After drying ($MgSO_4$) and concentration, distillation from a small amount of calcium carbonate afforded 1.60 g (84%) of **1a**–Cl: bp 63–64 °C (5 Torr); n^{19}_D 1.4580; IR (neat) 1600, 1251, 867, and 842 cm^{-1}; NMR (CCl_4) δ 6.37 (t, 1 H, J = 8 Hz), 2.2–0.8 (m, 9 H), and 0.23 (s, 9 H); exact mass, *m/e* 190.0971 (calcd for $C_9H_{19}ClSi$, 190.0946).

((*E*)-1-Chloro-2-cyclohexylethenyl)trimethylsilane (1b–Cl). Using the procedure described for the preparation of **1a**–Cl, 1.80 g (10 mmol) of **3b** was converted into 1.88 g (87%) of **1b**–Cl: bp 57–58 °C (0.5 Torr); n^{26}_D 1.4820; IR (neat) 1600, 1252, 865, 840, and 760 cm^{-1}; NMR (CCl_4) δ 6.22 (d, 1 H, J = 10 Hz), 2.3–1.0 (m, 11 H), and 0.22 (s, 9 H); exact mass, *m/e* 216.1112 (calcd for $C_{11}H_{21}ClSi$, 216.1102).

((*E*)-1-Bromo-1-hexenyl)trimethylsilane (1a–Br). According to the general hydroalumination procedure described above for the preparation of **1a**–Cl, 2.32 g (15 mmol) of **3a** contained in ether (7.5 mL) was treated with 16.5 mmol (10% excess) of diisobutylaluminum hydride (3.06 mL) and heated at 40 °C for 1 h. The hydroalumination product formed was diluted at 0 °C with ether (15 mL) and pyridine (2.4 mL). To the resultant yellow reaction mixture was added at −70 °C a solution of bromine (19.5 mmol, 1.5 M) in methylene chloride at such a rate as to maintain the temperature during the addition below −60 °C. The yellow slurry that formed was kept for an additional 15 min at −70 °C and then was poured slowly into a vigorously stirred mixture of 1 N sodium hydroxide (60 mL), ice (20 g), and *n*-pentane (15 mL). After shaking the mixture until it became clear, it was extracted with *n*-pentane. The combined organic extracts were washed successively with 1 N hydrochloric acid, a 20% aqueous solution of cadmium chloride (to remove small amounts of remaining pyridine), 1 N hydrochloric acid, and saturated aqueous sodium bicarbonate and then dried ($MgSO_4$). Distillation from a small amount of calcium carbonate afforded 3.17 g (90%) of **1a**–Br: bp 48 °C (1 Torr); n^{23}_D 1.4755; IR (neat) 1595, 1251, and 841 cm^{-1}; NMR (CCl_4) δ 6.71 (t, 1 H, J = 8 Hz), 2.1–0.9 (m, 9 H), and 0.25 (s, 9 H); exact mass, *m/e* 234.0413 (calcd for $C_9H_{19}BrSi$, 234.0440).

((*E*)-1-Bromo-2-cyclohexylethenyl)trimethylsilane (1b–Br). Following the procedure described above for the preparation of **1a**–Br, 1.80 g (10 mmol) of **3b** was subjected to hydroalumination–bromination. Distillation from calcium carbonate gave 2.51 g (96%) of **1b**–Br: bp 47–51 °C (10^{-3} Torr); n^{23}_D 1.5008; IR (neat) 1592, 1250, 860, and 840 cm^{-1}; NMR (CCl_4) δ 6.55 (d, 1 H, J = 10 Hz), 2.4–1.0 (m, 11 H), and 0.25 (s, 9 H); exact mass, *m/e* 260.0627 (calcd for $C_{11}H_{21}BrSi$, 260.0596).

((*E*)-1-Bromo-3,3-dimethyl-1-butenyl)trimethylsilane(1c–Br). Following the procedure described above for the preparation of **1a**–Br, 1.54 g (10 mmol) of **3c** yielded 2.01 g (86%) of **1c**–Br on hydroalumination–bromination: bp 54–55 °C (2 Torr); n^{23}_D 1.4821; IR (neat) 1570, 1251, and 845 cm^{-1}; NMR (CCl_4) δ 7.06 (s, 1 H), 1.12 (s, 9 H), and 0.32 (s, 9 H); exact mass, *m/e* 234.0422 (calcd for $C_9H_{19}BrSi$, 234.0440).

((*E*)-1-Bromo-2-cyelohexenylethenyl)trimethylsilane (1d–Br). Using the hydroalumination procedure described for the preparation of **1a**–Cl, 3.56 g (20 mmol) of **3d** was treated with 20 mmol of diisobutylaluminum hydride (no excess) and heated. To the resulting organoalane was added at 0 °C a 2 M solution of cyanogen bromide (22 mmol) in ether (dried over Drierite) at such a rate as to maintain the temperature below 10 °C. After stirring the mixture for 30 min at ambient temperature, it was transferred by means of the double-ended needle technique[27] to vigorously stirred, chilled, aqueous 6 N sodium hydroxide (100 mL). The reaction mixture was shaken vigorously to bring any remaining solid material into solution. The layers were separated, and the aqueous phase was extracted with *n*-pentane. The combined organic extracts were washed with aqueous 6 N sodium hydroxide and brine and dried ($MgSO_4$). Distillation from a small amount of calcium carbonate afforded 4.38 g (84%) of **1d**–Br: bp 46–47 °C (10^{-3} Torr); n^{20}_D 1.5235; IR (neat) 1628, 1592, 1260, 950, 904, and 855 cm^{-1}; NMR (CCl_4) δ 7.10 (s, 1 H), 5.53 (m, 1 H), 2.02 (m, 4 H), 1.63 (m, 4 H), and 0.21 (s, 9 H); exact mass, *m/e* 258.0418 (calcd for $C_{11}H_{19}BrSi$, 258.0439).

((*E*)-1-Iodo-1-hexenyl)trimethylsilane (1a–I). Following the general hydroalumination procedure described for the preparation of **1a**–Br, 7.72 g (50 mmol) of **3a** was reacted with 10.2 mL of diisobutylaluminum hydride (55 mmol). The resultant organoalane was diluted with ether (25 mL) and then treated at −70 °C with a solution of iodine (16.5 g, 65 mmol) in ether (100 mL) at such a rate as to maintain the temperature during the addition below −65 °C. The resulting brown reaction mixture was stirred for 1 h at −70 °C and then allowed to exotherm to 0 °C. After stirring for an additional 15 min at 0 °C, the yellow reaction mixture was slowly poured into a stirred mixture of 10% hydrochloric acid (200 mL) and ice (50 g). The two-phase mixture was shaken until the precipitate that had formed dissolved, and the mixture then was extracted with *n*-pentane. The combined organic extracts were washed successively with aqueous 1 N sodium hydroxide (50 mL), 1 M sodium thiosulfate, and brine and then dried ($MgSO_4$). Distillation from a small amount of calcium carbonate yielded 12.7 g (90%) of **1a**–I: bp 56–57 °C (1 Torr); n^{22}_D 1.5084; IR (neat) 1580, 1251, and 841 cm^{-1}; NMR (CCl_4) δ 7.12 (t, 1 H, J = 8 Hz), 2.1–0.9 (m, 9 H), and 0.26 (s, 9 H); exact mass, *m/e* 282.0321 (calcd for $C_9H_{19}ISi$, 282.0302).

((*E*)-1-Iodo-2-cyclohexylethenyl)trimethylsilane (1b–I). By a procedure similar to that described for the preparation of **1a**–I, 1.80 g (10 mmol) of **3b** was converted into 2.75 g (90%) of **1b**–I: bp 53–54 °C (10^{-4} Torr); n^{23}_D 1.5320; IR (neat) 1581, 1249, and 850 cm^{-1}; NMR (CCl_4) δ 6.96 (d, 1 H, J = 10 Hz), 2.4–1.0 (m, 11 H), and 0.25 (s, 9 H); exact mass, *m/e* 308.0458 (calcd for $C_{11}H_{21}ISi$, 308.0458).

((*E*)-1-Iodo-3,3-dimethyl-1-butenyl)trimethylsilane (1c–I). By a procedure similar to that described for the preparation of **1a**–I, 3.86 g (25 mmol) of **3c** yielded 6.07 g (85%) of **1c**–I: bp 64–65 °C (2 Torr); n^{23}_D 1.5183; IR (neat) 1555, 1251, and 845 cm^{-1}; NMR (CCl_4) δ 7.52 (s, 1 H), 1.02 (s, 9 H), and 0.25 (s, 9 H); exact mass, *m/e* 282.0278 (calcd for $C_9H_{19}ISi$, 282.0302).

((*Z*)-1-Chloro-1-hexenyl)trimethylsilane (2a–Cl). Using the procedure described above for the preparation of **1a**–Cl, 3.09 g (20 mmol) of **3a** was treated sequentially with diisobutylaluminum hydride and NCS. The reaction mixture containing the *E* chloride **1a**–Cl was poured slowly into vigorously stirred, chilled 10% hydrochloric acid (100 mL). The resulting mixture containing some solid material was shaken until the organic phase became clear. It then was extracted with three 10-mL portions of ether. The combined extracts were washed with 10% hydrochloric acid (10 mL), saturated aqueous sodium bicarbonate, and brine. After drying over $MgSO_4$ and filtration, the ethereal solution containing **1a**–Cl was stirred and treated three times at room temperature (water bath, cooled as needed) under a UV sunlamp (275 W) with 0.50 mL of pyridine followed by 1.0 mL of a 1.0 M solution of bromine in methylene chloride after 0, 30, and 60 min during a 90-min period. The reaction mixture was decanted from a gummy residue and washed with 10% hydrochloric acid (70 mL), 20% aqueous cadmium chloride (to remove traces of pyridine), water, 1 M sodium hydroxide, and brine. GLC analysis of the extract revealed, in addition to the *Z* chloride **2a**–Cl, a small amount of an unknown product of longer retention time. After drying ($MgSO_4$) and distillation there was obtained 3.08 g (81%) of **2a**–Cl: bp 74–77 °C (10 Torr); n^{20}_D 1.4517; IR (neat) 1610, 1252, and 838 cm^{-1}; NMR (CCl_4) δ 5.91 (t, 1 H, J = 7 Hz), 2.30 (d of t, 2 H, J = 7 Hz), 1.6–0.8 (m, 7 H), and 0.16 (s, 9 H); exact mass, *m/e* 190.0948 (calcd for $C_9H_{19}ClSi$, 190.0946).

((*Z*)-1-Chloro-2-cyclohexylethenyl)trimethylsilane (2b–Cl). Using the procedure described above for the preparation of **2a**–Cl, the crude *E* chloride **1b**–Cl derived from **3b** (20 mmol) was isomerized to afford 91% of **2b**–Cl: bp 70–71 °C; n^{19}_D 1.4798; IR (neat) 1610, 1251, and 838 cm^{-1}; NMR (CCl_4) δ 5.73 (d, 1 H, J = 8.5 Hz), 2.72 (m, 1 H), 2.0–1.0 (m, 10 H), and 0.17 (s, 9 H); exact mass, *m/e* 216.1078 (calcd for $C_{11}H_{21}ClSi$, 216.1102).

((*Z*)-1-Bromo-1-hexenyl)trimethylsilane (2a–Br). Using the procedure described above for the preparation of **2a**–Cl, the crude *E* bromide **1a**–Br derived from **3a** (30 mmol) was isomerized to yield 81% of **2a**–Br: bp 67–69 °C (4 Torr); n^{22}_D 1.4697; IR (neat) 1610, 1250, 880, and 840 cm^{-1}; NMR (CCl_4) δ 6.19 (t, 1 H, J = 6.5 Hz), 2.3–0.9 (m, 9 H), and 0.17 (s, 9 H); exact mass, *m/e* 234.0430 (calcd for $C_9H_{19}BrSi$, 234.0440).

((*Z*)-1-Bromo-2-cyclohexylethenyl)trimethylsilane (2b–Br). The reaction mixture containing the *E* bromide **1b**–Br derived from **3b** (25 mmol) was quenched in chilled 10% hydrochloric acid (125 mL) and then allowed to warm to room temperature. To the well-stirred two-phase mixture was added at room temperature (water bath) under ambient light conditions at the beginning and middle of a 60-min period 1.0 mL each time of a solution of bromine (1.25 M) in methylene chloride. The mixture was extracted with *n*-pentane, and the extract was washed with 10% hydrochloric acid (20 mL), 20% aqueous cadmium chloride (to remove traces of pyridine), water, aqueous sodium thiosulfate, 1 N sodium hydroxide, and brine. After drying ($MgSO_4$) and distillation there was obtained an 89% yield of **2b**–Br: bp 80–82 °C (2 Torr); n^{22}_D 1.4958; IR (neat) 1606, 1248, 884,

and 843 cm^{-1}; NMR (CCl_4) δ 5.99 (d, 1 H, J = 8 Hz), 2.9–1.1 (m, 11 H), and 0.15 (s, 9 H); exact mass, m/e 260.0603 (calcd for $C_{11}H_{21}BrSi$, 260.0596.

((*Z*)-1-Bromo-3,3-dimethyl-1-butenyl)trimethylsilane (2c-Br). Using the procedure described above for the preparation of **2b**–Br, the crude *E* bromide **1c**–Br derived from **3c** (5.0 mmol) was isomerized to afford 89% of **2c**–Br: bp 51–53 °C (5 Torr); n^{23}_D 1.4670; IR (neat) 1596, 1251, 897, and 844 cm^{-1}; NMR (CCl_4) δ 6.30 (s, 1 H), 1.23 (s, 9 H), and 0.16 (s, 9 H); exact mass, m/e 234.0458 (calcd for $C_9H_{19}BrSi$, 234.0440).

((*Z*)-1-Bromo-2-cyclohexenylethenyl)trimethylsilane (2d-Br). To a solution of **3d** (3.56 g, 20 mmol) in hexane (10 mL) was added dropwise at 25–30 °C diisobutylaluminum hydride (3.70 mL, 20 mmol). The reaction mixture was stirred for an additional 30 min at room temperature and then cooled in an ice bath and treated with a dried solution (Drierite) of cyanogen bromide (22 mmol, 2M) in ether. After stirring at ambient temperature for 1 h, the mixture was worked up as described above for the isolation of the corresponding *E* bromide **1d**–Br. Distillation from a small amount of calcium carbonate gave 4.37 g (84%) of **2d**–Br: bp 47–49 °C (10^{-3} Torr); n^{23}_D 1.5309; IR (neat) 1656, 1586, 1260, and 855 cm^{-1}; NMR δ 6.60 (s, 1 H), 6.00 (m, 1 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.62 (m, 4 H), and 0.18 (s, 9 H); exact mass, m/e 258.0433 (calcd for $C_{11}H_{19}BrSi$, 258.0439).

General Procedure for Lithium–Halogen Exchange Reactions of (1-Bromo- and 1-Iodo-1-alkenyl)silanes. To a solution of the (α-haloalkenyl)silane (10 mmol) in 20 mL of the appropriate solvent or solvent mixture at the indicated temperature was added a solution of *n*-butyllithium (11 mmol, 1.5–2.5 M) in hexane at such a rate as to limit the temperature rise to 5 °C. After stirring the reaction mixture for an appropriate length of time, it was treated dropwise with 1 mL of methanol, warmed to room temperature, and diluted with 10% hydrochloric acid. The resultant (1-alkenyl)silane was extracted with *n*-pentane, dried ($MgSO_4$), and analyzed by GLC using a hydrocarbon as an internal standard to measure the yield. The isomeric purity of the compound was determined on a glass capillary column (SE-30; 50 m) by comparing the retention times of the peaks observed with those from authentic samples of the corresponding ((*E*)- and (*Z*)-1-alkenyl)silanes. The results of these experiments are summarized in Table II.

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Registry No.—1-Hexyne, 693-02-7; cyclohexylacetylene, 931-48-6; *tert*-butylacetylene, 917-92-0; 1-ethynylcyclohexene, 931-49-7.

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Reaction of 1,1,2-Trichloro-1,2,2-trifluoroethane and Other Fluorohalocarbons with Aluminum Halides in the Presence and Absence of Additives. Distinction in Carbonium Ion Character and Reaction Conditions between Substitution and Isomerization

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In the reaction of $CF_2ClCFCl_2$ with aluminum chloride, the addition of carbon disulfide, trichloroethylene, methylene chloride, *n*-hexane, cyclohexane, etc., was found to be effective in inhibiting the isomerization into CF_3CCl_3 without significantly retarding the substitution, which gives CF_2ClCCl_3. Cyclohexane was also used for similar purposes to obtain CF_3CClBr_2 from CF_3CFBr_2, CF_2BrCCl_2Br from $CF_2BrCFClBr$, $CF_2BrCClBr_2$ from $CF_2BrCFClBr$ (+ $AlBr_3$), and $CF_2ClCBrCl_2$ from $CF_2ClCFCl_2$ (+ $AlBr_3$). In each of these reactions cyclohexane–methylcyclopentane equilibration as well as formation of a small amount of a hydride-transfer product, such as $CF_2ClCHCl_2$, was noted. In the treatment of $CF_2ClCFCl_2$ with aluminum chloride, the isomerization was never complete as far as vigorous stirring was continued. Discontinuation of the stirring afforded aluminum fluoride precipitates effective for the isomerization of fluorohalocarbons. Reactions of $CF_2ClCFCl_2$ with aluminum halides in the presence of halomethanes and similar reactions of $CF_2BrCFClBr$ were also studied. For example, the reaction $CF_2ClCFCl_2 + CCl_4 + AlCl_3$ yielded CF_2ClCCl_3 and CF_2Cl_2 as the main products, but only a minor amount of CF_3CCl_3. The substitution reaction is considered to proceed in solution via the ion pair $CF_2ClC^+Cl_2 \cdot AlFCl_3^-$ without rearrangement. The isomerization is considered predominantly a surface reaction, for which the following reactions are suggested to proceed when the carbonium ions are dissociated from the counteranions anchored on (or inside of) the solid surface: $CF_2ClCFCl_2 + {}^+CF_2CCl_3 \rightarrow CF_2ClC^+Cl_2 + CF_3CCl_3$; $CF_2ClC^+Cl_2 \rightleftarrows {}^+CF_2CCl_3$.

Substitution[1,2a] and isomerization[2b,3a] generally occur when chlorofluorocarbons are treated with aluminum chloride. However, the relationship between these two types of reactions, as well as the relationship between the isomerization and the disproportionation[3b] of chlorofluorocarbons, does not seem to be well understood. In repeated treatment of $CF_2ClCFCl_2$ with aluminum chloride for the preparation of CF_2ClCCl_3[4] (used as the precursor of $CF_2{=}CCl_2$),[5] we noted that the isomerization to CF_3CCl_3 sometimes did not occur when partially deteriorated aluminum chloride[6a] was used, while the substitution, which gives CF_2ClCCl_3, always occurred without failure. This appeared to give a clue for understanding the difference in nature between these two reactions. Hence, the reaction of $CF_2ClCFCl_2$ with aluminum chloride and related reactions have been studied in some detail in order to gain a mechanistic insight for these reactions as well as to find better ways for separate utilization of the two types of reactions.

Results

The reaction of $CF_2ClCFCl_2$ with aluminum chloride showed a marked stirring effect. Thus the isomerization was never complete as far as vigorous stirring[6b] was continued (for 2, 3, 5, and 7 h) with refluxing. When stirring and external heating were discontinued, refluxing ceased temporarily, but soon the reaction mixture began to reflux again, showing an active occurrence of the isomerization. Thirty minutes after the initial vigorous stirring had been stopped, unchanged $CF_2ClCFCl_2$ was practically absent from the reaction mixture. With less efficient stirring the isomerization was complete in a few hours even if the stirring was uninterrupted.

The resulting bulky precipitates of AlF_xCl_{3-x} had a catalytic activity for the isomerization and disproportionation of fluorohalocarbons. Use of such precipitates provides an efficient preparative method of CF_2ClCCl_3 by isomerization of $CFCl_2CFCl_2$ (a commercial sample containing CF_2ClCCl_3). The experimental procedure is described in a previous paper.[5] Direct treatment of $CFCl_2CFCl_2$ with aluminum chloride gives unsatisfactory results.[4,7,8]

Active mixtures of the reaction of $CF_2ClCFCl_2$ with aluminum chloride induced smooth isomerization of CF_2BrCF_2Br to CF_3CFBr_2[9] and subsequent reactions as shown in Figure 1. This smooth isomerization of CF_2BrCF_2Br is in marked contrast to the existence of long and variable induction periods (20–60 h, 14 h, 18 h, 33 h, >65 h: discontinued, 4 days)[10] in direct treatment of CF_2BrCF_2Br with aluminum chloride under refluxing conditions.[11] The isomerization of CF_2BrCF_2Br occurred without significant induction period and was even faster than the isomerization of $CF_2ClCFCl_2$, where a mixture of CF_2BrCF_2Br and $CF_2ClCFCl_2$ was treated with aluminum chloride.

Reactions of $CF_2ClCFCl_2$ (100 g) with aluminum chloride (10 g) in the presence of additives (30 mL) were also studied. In the presence of nitrobenzene, tetrahydrofuran, or triethylamine, neither the isomerization nor the substitution was observed, except that a small amount of CF_2ClCCl_3 was found in the case where triethylamine was used.[12] In the presence of benzene, chlorobenzene, trichloroethylene, cyclohexane, *n*-hexane, carbon disulfide,[13] and methylene chloride, only the substitution was observed. In the presence of tetrachloroethylene, bromine, carbon tetrachloride, and chloroform, both the isomerization and substitution were observed, though the proportion of the isomerization was greatly decreased in some cases (vide infra).

The reaction where cyclohexane was used as additive (Table I) is interesting because, although the isomerization of $CF_2ClCFCl_2$ was practically inhibited, the isomerization of cyclohexane was allowed to occur. The rate of approaching cyclohexane–methylcyclopentane equilibrium was, however, only moderate.[14] The formation of $CF_2ClCHCl_2$ was confirmed by the ^{19}F NMR spectrum of a $CF_2ClCHCl_2$-containing fraction obtained from this reaction and distilling at 53–76 °C, an authentic sample, and a mixture of the two. A further confirmation was obtained from the mass spectrum, which is identical with that of the authentic sample in GC–mass spectroscopy.

The reactions where carbon tetrachloride and chloroform were used as additives were characterized by the occurrence of exchange of chlorine and fluorine between molecules of the fluoroethane and halomethane at the expense of the isomerization of $CF_2ClCFCl_2$. In the reaction where chloroform was the additive, there was observed an induction period (1.5 h)

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Table I. Reaction of Fluorohalocarbons with Aluminum Chloride or Bromide in the Presence of Cyclohexane[a,b]

Substrate RF	$AlCl_3$, g	Time, h	Product distribution, %[c] RF[d]	RCl	RBr	RH	R'F[e]
$CF_2ClCFCl_2$	30	23	27	70		2	0.3
$CF_2ClCFCl_2$	25 ($AlBr_3$)	5[f]	70	0.6	26	3[g]	0.3
$CF_2BrCFClBr$	10	4	76	21		1[h]	2
$CF_2BrCFClBr$	24 ($AlBr_3$)	2.5[i]	64		24[j]	1[h]	9
CF_3CFBr_2	20	20	43	49		8	
$CFCl_3$	10	4[k]	72	28			
$CFCl_3$[l]	10	5[k]	70	30			
$CF_2ClCFCl_2$[l]			100				
$CF_2ClCFCl_2$[m]	10	3	98	2.5			
$CF_2BrCFClBr$[m]			67	32			1

[a] Aluminum chloride or bromide was added to a solution of 100 g of the substrate (or combined substrates) in 30 mL of cyclohexane, and unless otherwise stated the resulting mixture was refluxed for the indicated period of time with stirring. [b] The formation of methylcyclopentane was observed unless otherwise stated. [c] The product distribution was determined from ^{19}F NMR peak heights. The ratio $CCl_4/CFCl_3$ was determined by GC. [d] Unchanged substrate. [e] CF_3CCl_3 (from $CF_2ClCFCl_2$) or CF_3CClBr_2 (from $CF_2BrCFClBr$). [f] Initial heating induced a vigorous reaction. [g] The ratio $CF_2ClCHCl_2/CF_2ClCCl_2Br$ was determined from the ratio of ^{19}F NMR areas recorded on an expanded scale. [h] A small concentration of this compound ($CF_2BrCHClBr$) was practically undetectable by ^{19}F NMR because of signal multiplicity. See the footnote *m* of Table II. The ratio $CF_2BrCHClBr/CF_2BrCCl_2Br$ or $CF_2BrCHClBr/CF_2BrCClBr_2$ was determined from the GC area ratio assuming equal molar sensitivity. [i] Only for the last 20 min of this period the reaction mixture was heated (~60 °C). Each addition of aluminum bromide (in two portions in a 1-h interval) had induced a vigorous reaction. [j] In addition to this compound ($CF_2BrCClBr_2$), a compound (2%) which was suspected to be CF_2ClCBr_3 was formed. See footnote *g* of Table II. [k] Methylcyclopentane was not found in the resulting mixture. [l] Mixture of equal weights. [m] Equimolar mixture.

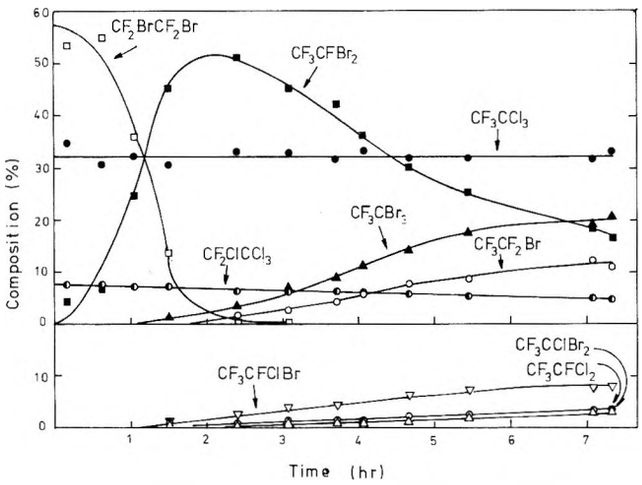

Figure 1. Reaction profile of room temperature treatment of CF_2BrCF_2Br with active precipitate obtained from $CF_2ClCFCl_2$ and aluminum chloride. (The active precipitate together with the accompanying liquid was placed in an NMR tube and the tube cooled with ice and sealed after addition of CF_2BrCF_2Br.)

for the formation of CF_3CCl_3 (and CHF_3) probably due to ethanol present as stabilizer in chloroform, while CF_2ClCCl_3 was formed from the beginning. After this period a brisk evolution of a gas (mostly CHF_3)[15] occurred over a short period (0.2 h), leaving a solidified mixture whose main component was hexachloroethane. On the other hand, when the reaction in which carbon tetrachloride was the additive was followed, there was observed a gradual and steady evolution of a gas (CF_2Cl_2 and small amounts of $CFCl_3$ and CF_3Cl).

In the reaction system $CF_2ClCFCl_2 + CFCl_3 + AlCl_3$, the initial reaction was the substitution reaction and disproportionation of $CFCl_3$. The formation of CF_2ClCCl_3 became appreciable (0.4%) only after 80% of the $CFCl_3$ had been converted into CCl_4 and CF_2Cl_2.

When aluminum bromide (10 g) was added to a solution of $CF_2BrCFClBr$ (100 g) in carbon tetrachloride (200 mL), an exothermic reaction occurred. The determined fluoroethane distributions of the resulting mixture after 4 min and 3.5 h (given in this order) were as follows: CF_3CClBr_2, 85, 86%; CF_2BrCCl_2Br, 8, 3%; $CF_2ClCClBr_2$, 7, 11%. Isomerization of CF_2BrCCl_2Br to $CF_2ClCClBr_2$, besides isomerization of $CF_2BrCFClBr$ to CF_3CClBr_2,[16] is apparent. It is also evident that the amount of CF_2BrCCl_2Br initially formed was equal to or greater than the amount of $CF_2ClCClBr_2$ initially formed.

Discussion

Substitution Reaction and Relative Carbonium Ion Stability. The rate of the substitution reaction is controlled by the solubilization of aluminum chloride as shown by the fact that, in spite of their considerable difference in reactivity under competitive conditions (Table I), $CF_2ClCFCl_2$ and $CFCl_3$ undergo the substitution reaction at comparable rates when individually treated. The first step of the substitution reaction, in the early stages, is considered the formation of ion pair $CF_2ClCCl_2^+ \cdot AlFCl_3^-$ from interaction with monomeric aluminum chloride, which exists in equilibrium with the dimer, the major soluble species. The decomposition of the ion pair into CF_2ClCCl_3 and $AlFCl_2$ does not seem to be spontaneous (in view of the formation of condensation products at the expense of CF_2ClCCl_3 in the presence of benzene).

The absence of rearrangement in the substitution reactions of this type is indicated by the formation of CF_2ClCCl_2Br and CF_2BrCCl_2Br as the exclusive substitution products of the following reactions:[17]

$$CF_2ClCFCl_2 \xrightarrow{AlBr_3\ (cyclohexane)} CF_2ClCCl_2Br$$

$$CF_2BrCFClBr \xrightarrow{AlCl_3\ (cyclohexane)} CF_2BrCCl_2Br$$

Since CF_2BrCCl_2Br is thermodynamically less stable than $CF_2ClCClBr_2$, as shown by the observation that the former was converted into the latter under isomerizing conditions, the generality of the absence of rearrangement in the substitution reactions of this type is little doubted.[17]

The relative stabilities of fluorohalocarbonium ions can be inferred from the reactivities of fluorohalocarbons with re-

spect to the substitution with aluminum halides. For example, $CF_2ClC^+Cl_2$ is suspected to be more stable than $^+CF_2CCl_3$ from the much greater reactivity of $CF_2ClCFCl_2$ as compared with that of CF_3CCl_3. This view is supported by the much greater reactivity of the chlorine atoms of the CCl_3 group of CF_2ClCCl_3 than that of the chlorine atom of the CF_2Cl group of this compound with respect to the substitution of fluorine for chlorine with antimony fluorides.

From similar considerations, a carbonium ion having α-chlorine is generally inferred to be more stable than the corresponding carbonium ion having α-fluorine (at least for the ion pair state).[18] The reverse of this inference is often assumed.[19] However, the relative *overall* order of α-fluorine and α-chlorine in stabilizing the carbonium ion apparently has not been established, though greater "back-donating ability" [20] of α-fluorine is unequivocal.

Nature of Isomerization Catalyst and Effect of Stirring. The behavior of CF_2BrCF_2Br on treatment with aluminum chloride can be explained in terms of the view[21,22] that catalytically active aluminum fluoride is formed from aluminum chloride by the substitution reaction with $CF_2ClCFCl_2$ and other fluorohalocarbons. The catalytic activity of aluminum chloride as such for the isomerization of CF_2BrCF_2Br seems to be negligibly small. The substitution of chlorine for fluorine in CF_2BrCF_2Br also does not occur before the isomerization is induced. On the other hand, the isomerization product CF_3CFBr_2 undergoes smooth substitution with aluminum chloride to give CF_3CClBr_2 (Table I). Hence, once the isomerization is started somehow in the presence of aluminum chloride, the isomerization and substitution proceed rapidly.

The increase in catalytic activity with an increase in the extent of substitution of fluorine for chlorine of aluminum chloride is basically attributable to the increase in the stable coordination number around the aluminum atom (while the valence of aluminum is kept at three). The stable coordination number is six where the coordinating atoms are fluorine[23] and four where the coordinating atoms are chlorine. Hence, with aluminum fluoride even the solid surface has a coordinating ability,[24,25] whereas with aluminum chloride only the monomeric species is capable of coordination. Aluminum chloride fluorides may have intermediate properties.

The stirring effect on the isomerization is also explicable in terms of the catalytic activity of aluminum fluoride formed by the substitution reaction. The solubility of aluminum chloride in fluorohalocarbons is low in comparison with the rate of its consumption by the substitution reaction of $CF_2ClCFCl_2$, and the supply of aluminum chloride to the solution is greatly dependent on the efficiency of stirring (and particle size). When the stirring is stopped or its speed slowed down after vigorous stirring has been continued for some time, the supply of aluminum chloride is greatly reduced. Then the x value denoting the average composition AlF_xCl_{3-x} of the solid surface and soluble species will sharply rise as the substitution reaction proceeds and approach three (or possibly to a somewhat lower value), giving active aluminum fluoride.

Two conceivable modes of interaction of such a solid surface with RF is reversible (eq 1) and irreversible (eq 2) ionization of the latter:

$$RF + AlF_3 \rightleftarrows R^+ + AlF_4^- \quad (1)$$

$$R\cdot^+AlF_4^- \rightleftarrows R^+ + AlF_4^- \quad (2)$$

where AlF_3 represents an active point of the solid surface and AlF_4^- the corresponding fluoride-coordinated form. The mode (eq 2) action results in a catalytic activity if the carbonium ion abstracts a fluoride ion (and/or a chloride ion) from a neutral molecule. Irreversible ionization is also expected to occur by such processes as the occlusion of the fluoride ion inside of an aluminum fluoride cluster.

Isomerization and Related Reactions. The results of the reaction of $CF_2ClCFCl_2$ with aluminum chloride in the presence of additives indicate that the carbonium ion character is much greater in the isomerization than in the substitution reaction. More specifically, the necessity of a more reactive carbonium ion or related species and/or a longer existence of such an intermediate are suggested for the isomerization.

For the isomerization of $CF_2ClCFCl_2$ the following mechanism is suggested,[26] where the carbonium ions[27] apparently have to be dissociated from the counteranions for the reaction to proceed. This mechanism constitutes a chain process, though the chain nature of the reaction may be obscured by the interaction of carbonium ions[27] with counteranions.

$$CF_2ClCFCl_2 + {}^+CF_2CCl_3 \rightarrow CF_2ClC^+Cl_2 + CF_3CCl_3$$

$$CF_2ClC^+Cl_2 \rightleftarrows {}^+CF_2CCl_3$$

According to this mechanism the isomerization involves intermolecular transfer of fluoride[28] and intramolecular chloride shift (mechanistically, shift of chlorine having a partial positive charge), while related disproportionation reactions involve intermolecular transfer of fluoride[28] and chloride. It is implied that the fluoride transfer would be considerably easier than the chloride transfer.

The isomerization of CF_2BrCF_2Br is similarly represented by the following equations.

$$CF_2BrCF_2Br + {}^+CF_2CFBr_2 \rightarrow CF_2BrC^+FBr + CF_3CFBr_2$$

$$CF_2BrC^+FBr \rightleftarrows {}^+CF_2CFBr_2$$

The isomerization of CF_2BrCF_2Br, once appropriate isomerizing conditions are realized, is faster than that of $CF_2ClCFCl_2$ as confirmed by the reaction $CF_2ClCFCl_2 + CF_2BrCF_2Br + AlCl_3$.[29] This is attributable to easier intramolecular bromide shift, as compared with intramolecular chloride shift, coupled with the existence of fluoride acceptors sufficiently strong to abstract fluoride from CF_2BrCF_2Br as well as from $CF_2ClCFCl_2$.[30]

The retardation of isomerization of $CF_2ClCFCl_2$ by carbon tetrachloride is ascribed to chloride transfer from carbon tetrachloride in competition with fluoride transfer from $CF_2ClCFCl_2$. $CFCl_3$ is formed by fluoride transfer to $^+CCl_3$ from $CF_2ClCFCl_2$.

$$CCl_4 + CF_2ClC^+Cl_2 \rightarrow {}^+CCl_3 + CF_2ClCCl_3$$

$$CF_2ClCFCl_2 + {}^+CCl_3 \rightarrow CF_2ClC^+Cl_2 + CFCl_3$$

Likewise CF_2Cl_2 is considered as resulting from fluoride transfer to $^+CFCl_2$ from $CF_2ClCFCl_2$ and from $CFCl_3$. The importance of the latter process is evident from the results of the reaction $CF_2ClCFCl_2 + CFCl_3 + AlCl_3$, where the disproportionation, as well as the substitution reaction, of $CFCl_3$ occurred in preference to the formation of CF_2ClCCl_3.

$$CFCl_3 + {}^+CFCl_2 \rightarrow {}^+CCl_3 + CF_2Cl_2$$

$$CFCl_3 + {}^+CCl_3 \rightarrow {}^+CFCl_2 + CCl_4$$

A straightforward explanation for the inhibiting action of cyclohexane and n-hexane and for the formation of $CF_2ClCHCl_2$ is hydride transfer, a well-known mode of reac-

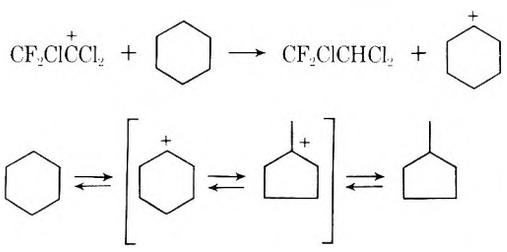

Table II. Physical Data and Method of Preparation of Fluorohalocarbons

Compd	Registry no.	Bp, °C	n^{20}_D or fp, °C	^{19}F NMR, ppm[a] CF_3	CF_2	CF	Starting compd and reagent[b]	Registry no.
CF_3CCl_3	354-58-5	45–47	1.3599	3.0			$CF_2ClCFCl_2$, i	
CF_3CCl_2Br	354-50-7	67	25	1.8			c	
CF_3CClBr_2	754-17-6	90–91	45	0.6			CF_3CFBr_2, ii	
CF_3CBr_3	354-48-3	115	69	−0.5			CF_2BrCF_2Br, iv	
CF_3CFBr_2	27366-23-8	46.5	1.3708	3.3[d]		−1.3[d]	CF_2BrCF_2Br, iv	
$CF_2ClCHCl_2$	354-21-2	71	1.3918		−16.0[e]		$CHCl_2CCl_3$, vi	76-01-7
CF_2ClCCl_3	76-11-9	92–93	40.5		−14.2		*f*	
CF_2ClCCl_2Br	50994-70-2	111–112.5	49		−16.0		$CF_2ClCFCl_2$, v	
$CF_2ClCClBr_2$	25856-30-8	137	72		−17.4		CFClBrCFClBr, iii	
CF_2BrCCl_2Br	558-57-6	136	45		−22.9		$CF_2{=}CCl_2$, vii	79-35-6
$CF_2BrCClBr_2$[g]	66270-59-5	85[h]	58		−24.4		$CF_2BrCFClBr$, v	
CF_2BrCF_2Br[i]	124-73-2		1.3704		−15.7			
$CF_2BrCFClBr$	354-51-8	92	1.4282		−18.5[j]	−10.2	$CF_2{=}CFCl$, vii	79-38-9
					−20.2[j]			
$CF_2ClCFCl_2$[k]	76-13-1		1.3587		−11.1	−7.1		
$CFCl_2CFCl_2$	76-12-0	91.5–93	25			−11.5	CCl_3CCl_3, vi	67-72-1
$CFCl_2CCl_3$	354-56-3	139	98			−16.1	CCl_3CCl_3, vi	
CFClBrCFClBr		138–138.5	30			−14.7[l]	CFCl=CFCl, vii	598-88-9
						−15.6[l]		

[a] 20% solution in carbon tetrachloride. Upfield relative to external CF_3CO_2H. Chemical shifts and coupling constants for compounds not isolated pure are given in footnote *m*. [b] (i) $AlCl_3$; (ii) $AlCl_3$ + cyclohexane; (iii) active mixture obtained from $CF_2ClCFCl_2$ + $AlCl_3$; (iv) $AlBr_3$; (v) $AlBr_3$ + cyclohexane; (vi) SbF_3 + $SbCl_5$; (vii) Br_2. [c] A mixture of 100 g of CF_3CFBr_2, 72 g of CF_3CCl_3, and 20 g of aluminum chloride was refluxed for a total of 70 h, and 8.6 g of CF_3CBrCl_2 was isolated. [d] J = 10 Hz. [e] J_{FH} = 6 Hz. [f] See the text. [g] Contaminated with ~7% of a compound showing a singlet at −18.4 ppm and thought to be CF_2ClCBr_3. [h] At 65 mm. [i] Daiflon 114B2, donated by Daikin Co. Ltd. [j] An AB pattern, J = 167 Hz; each peak further split into a doublet, J = 14 and 13 Hz. See J. J. Drysdale and W. D. Phillips, *J. Am. Chem. Soc.*, **79**, 319 (1957). [k] Daiflon S3, a commercial product. [l] The value −14.7 for the meso form and the value −15.6 for the *d,l* pair. See D. S. Thompson, R. A. Newmark, and C. H. Sederholm, *J. Chem. Phys.*, **37**, 411 (1962). [m] $CF_3CFClBr$ (the cold trap condensate of a reaction $CF_2ClCFCl_2$ + CF_2BrCF_2Br + $AlCl_3$, CCl_4 solution): 5.2 (doublet), −1.6 (quadruplet), J = 8 Hz. CF_3CFCl_2 (same as before): 6.2 (doublet), − 1.4 (quadruplet), J = 6 Hz. CF_3CF_2Br (same as before): 7.4 (triplet), −8.1 (quadruplet), J = 2.4 Hz. $CF_2BrCHClBr$ (a fraction boiling at 53–81 °C (65 mm), neat): an AB pattern, −26.3, −23.0, J = 161 Hz; each peak further split into a doublet, J_{FH} = 6 and 8 Hz; see the literature given in footnote *j*. CF_3CHBr_2 (a fraction boiling at 68–73 °C, neat): −3.4, J_{FH} = 6 Hz.

tion in the liquid phase[31] as well as in the gas phase.[32] This also explains why the isomerization of cyclohexane, which is not induced by aluminum chloride alone,[33] occurs in the reaction system.

Experimental Section

^{19}F NMR spectra were recorded on a JNM-C-60 during the early period of the study and on a Hitachi R-20BK during the later period. Unless otherwise stated, the relative amounts of fluorine compounds (including those for the figures) were determined from peak heights on charts recorded from full-range sweeps of 90 or 100 ppm, where signals of fluorohalocarbons were practically sharp lines. (The performance of the sliding resistor used in the scanning mechanism was critical for reproducibility in peak height on each of the instruments.) It was assumed that the ratios of peak heights are equal to the ratios of the numbers of the corresponding ^{19}F nucleus. That this method gives results reasonably accurate for the present purpose was confirmed in the following cases, where the ranges obtained from seven to ten sweeps each were compared with the theoretical values (given in parentheses). The CF_3CCl_3 percentages for neat mixtures of CF_3CCl_3 and $CF_2ClCFCl_2$ were 19.5–21.1 (19.8), 36.6–41.9 (39.6), 56.9–60.1 (59.4), and 76.3–78.2 (79.2). The CF_2ClCCl_3 percentages for solutions of CF_2ClCCl_3 and $CF_2ClCFCl_2$ in tetrachloroethylene were 11.4–13.4 (12.2) and 36.7–41.2 (40.7). The CF_2BrCF_2Br percentage of a neat mixture of CF_2BrCF_2Br and $CF_2ClCFCl_2$ was 40.5–43.4 (41.9).

GC works were performed using a 4-m column of Silicon-DC 550. The relative amount of two compounds (e.g., methylcyclopentane/cyclohexane) was determined from peak heights using reference solutions containing known amounts of the two compounds.

Temperatures are uncorrected. For withdrawal of aliquots of reaction mixtures which contained solids (aluminum chloride) and tended to solidify (due to the presence of CCl_3CCl_3), a special pipet was used, which has a relatively large bore on the bottom and contains a glass ball. For most of the experiments sublimed aluminum chloride powder (Merck 1081, as received) was used. The preparation and source of fluorohalocarbons are summarized in Table II.

Treatment of 1,1,2-Trichloro-1,2,2-trifluoroethane ($CF_2ClCFCl_2$) with Aluminum Chloride in Preparative Scale. (A) In the Presence of Carbon Tetrachloride. A mixture of $CF_2ClCFCl_2$ (1000 g, 5.34 mol), carbon tetrachloride (300 mL, 479 g, 3.11 mol), and aluminum chloride (100 g, 0.75 mol) was refluxed with stirring for 5.5 h, during which time the refluxing temperature increased from 55 to 74 °C. Volatile products were collected in a trap cooled with dry ice–acetone. Workup and fractional distillation afforded an isomeric mixture (124 g) of $CF_2ClCFCl_2$ (77%) and CF_3CCl_3 (23%), carbon tetrachloride (193 g), and CF_2ClCCl_3 (576 g, 53% based on charged $CF_2ClCFCl_2$). The cold trap condensate, whose main ingredient was CF_2Cl_2, steadily increased its weight (final weight 270 g).

(B) In the Presence of Carbon Disulfide. A mixture of $CF_2ClCFCl_2$ (1000 g, 5.34 mol), carbon disulfide (200 mL, 256 g), and aluminum chloride (200 g, 1.50 mol) was refluxed for 20.5 h with stirring. Workup and fractional distillation afforded CS_2–$CF_2ClCFCl_2$ azeotrope (bp 38 °C, 604 g), $CF_2ClCFCl_2$ (89 g, bp 47 °C), and CF_2ClCCl_3 (415 g, 38%). As the content of $CF_2ClCFCl_2$ in the azeotrope was determined as 63% by GC, the total amount of recovered $CF_2ClCFCl_2$ was calculated to be 470 g. Hence the yield of CF_2ClCCl_3 corresponds to 72% of unrecovered $CF_2ClCFCl_2$.

(C) In the Presence of *n*-Hexane. From a similar experiment where the additive was *n*-hexane (200 mL, 134 g) and the refluxing time was 24 h were obtained $CF_2ClCFCl_2$ (487 g), *n*-hexane (52 g), and CF_2ClCCl_3 (347 g, 32% and 62% yield based on charged and unrecovered $CF_2ClCFCl_2$, respectively).

Isomerization of 1,2-Dibromo-1,2-dichloro-1,2-difluoroethane (CFClBrCFClBr). A mixture of $CF_2ClCFCl_2$ (200 g) and aluminum chloride (20 g, 0.15 mol) was refluxed with efficient stirring for 2 h, after which time an exothermic isomerization of $CF_2ClCFCl_2$ into CF_3CCl_3 was induced by discontinuation of stirring and external heating. CFClBrCFClBr (218 g, 0.745 mol) was added, but the isomerization into $CF_2ClCClBr_2$ occurred only to a small extent in 18 min. (The failure of a smooth isomerization is suspected to be due to possible impurities, such as ethanol, in the substrate.) The resulting mixture was refluxed for 50 min and left standing overnight. The solidified mixture no longer contained CFClBrCFClBr. Hydrolysis,

workup, and fractional distillation afforded $CF_2ClCClBr_2$ (93 g, 43%); bp 137 °C; fp 72 °C. The sample was found to contain ~3% CF_2BrCCl_2Br.

Registry No.—*meso*-CFClBrCFClBr, 42067-62-3; *dl*-CFClBrCFClBr, 42067-63-0; $CFCl_3$, 75-69-4; $AlCl_3$, 7446-70-0; $AlBr_3$, 7727-15-3.

Supplementary Material Available: Product yields of the reaction of $CF_2ClCFCl_2$ with aluminum chloride in the presence of additives (Table III); product distributions of the reactions of $CF_2ClCFCl_2$ and CF_2BrCF_2Br with aluminum halides in the presence of halomethanes (Table IV); and reaction profiles of the following reaction systems: (i) $CF_2ClCFCl_2$ + CF_2BrCF_2Br + $AlCl_3$; (ii) $CF_2ClCFCl_2$ + $AlCl_3$; (iii) $CF_2ClCFCl_2$ + a small proportion of $(C_2H_5)_3N$ + $AlCl_3$; (iv) $CF_2ClCFCl_2$ + CCl_4 + $AlCl_3$ (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Reactions of the type $CF_2ClCFCl_2$ + $AlCl_3$ → CF_2ClCCl_3 + $AlFCl_2$ are often referred to as halogen exchange. In this paper, however, the use of the term "halogen exchange" for such reactions is confusing because this term rather implies results such as the formation of CF_2ClCCl_3 and $CFCl_3$ from $CF_2ClCFCl_2$ and CCl_4 under aluminum fluoride catalysis, from which reactions of the above type have to be distinguished from the mechanistic point of view.

(2) (a) M. Hudlicky, "Chemistry of Organic Fluorine Compounds", 2nd ed, Ellis Horwood, Chichester, England, 1976, pp 234–236; (b) *ibid.*, pp 501–503.

(3) (a) E. Forche, *Methoden Org. Chem.*, **5**, part 3, 351–353 (1962); (b) *ibid.*, **5**, part 3, 354–357 (1962).

(4) W. T. Miller, Jr., E. W. Fager, and P. H. Griswald, *J. Am. Chem. Soc.*, **72**, 705 (1950).

(5) K. Okuhara, *J. Org. Chem.*, **41**, 1487 (1976).

(6) (a) A portion of the contents left unused in a reagent bottle whose seal was broken about 10 years before that time. (b) A 8 × 2 cm crescent polytetrafluoroethylene blade at ~600 rpm for a 500- or 1000-mL flask.

(7) M. Hudlicky and L. Lejhancova, *Collect. Czech. Chem. Commun.*, **30**, 2491 (1965).

(8) Treatment of $CFCl_2CFCl_2$ with aluminum bromide gives a higher yield of CF_2ClCCl_3: M. Hudlicky, Czechoslovakian Patent 113 114 (1969); *Chem. Abstr.*, **73**, 87406r (1970). See also ref 2, p 724.

(9) For the preparation of CF_3CFBr_2, CF_2BrCF_2Br was treated with aluminum bromide: P. Piccardi, M. Modena, and E. Santoro, *J. Chem. Soc., Perkin Trans. 1*, 1146 (1972).

(10) The isomerization was detected by a characteristic pattern in the recorded temperature curve. In each run a mixture of 100 g of CF_2BrCF_2Br and 10 g of aluminum chloride was refluxed with magnetic stirring.

(11) Long induction periods are implied in descriptions of previous experiments for this reaction system: (a) D. J. Burton, Ph. D. Thesis, Cornell University, 1961, p 101; (b) D. J. Burton and L. J. Kehoe, *J. Org. Chem.*, **35**, 1339 (1970).

(12) When a smaller portion of triethylamine was added (1 mL to 500 g of $CF_2ClCFCl_2$), the isomerization began to occur after an induction period (~3 h).

(13) The isomerization of $CF_2BrCFClBr$ was not inhibited by carbon disulfide, though a considerable retardation was apparent.

(14) When a mixture of $CF_2ClCFCl_2$ (100 g), cyclohexane (30 mL), and alumimum chloride (10 g) was refluxed, the percentage of methylcyclopentane determined by gas chromatography changed as follows: 8% (1 h), 14% (2 h), 16% (3 h), 17% (4 h), 17.5% (5 h), and 18% (21 h; 56 °C). When methylcyclopentane was used in place of cyclohexane, the percentage changed as follows: 68% (1 h), 40% (2 h), 27% (3 h), 22% (4 h), 20% (5 h), and 19% (21 h; 56 °C).

(15) The main portion of the gas did not condense in a dry ice–acetone cooled trap and was identified as CHF_3 (bp −84 °C) from its infrared spectrum, which is identical with the published one: J. H. Simons, *Fluorine Chem.*, **2**, 472 (1954).

(16) The isomerization of $CF_2BrCFClBr$ is described in ref 11a (p 107, 109) and 11b.

(17) The absence of $CF_2ClCClBr_2$ in the mixture obtained from the reaction of $CF_2BrCFClBr$ with aluminum chloride in the presence of cyclohexane was confirmed. In the corresponding reaction with aluminum bromide, however, there was evidence for the formation of CF_2ClCBr_3 besides $CF_2BrCClBr_2$ (see Table II, footnote *g*). A small portion of ion pair $CF_2BrC^+ClBr{\cdot}AlFBr_3^-$ probably dissociates. Bromide abstraction of the rearranged carbonium ion $CF_2ClC^+Br_2$ from $AlFBr_3^-$ gives CF_2ClCBr_3 together with $AlFBr_2$.

(18) Since in the tight ion pair the positive charge is expected to concentrate near the counteranion, that is, on the carbonium carbon to a greater extent than in the dissociated state, the importance of the electron-donating mesomeric effect relative to the electron-withdrawing inductive effect appears to be greater in the dissociated state than in the tight ion pair. Hence, although the overall positive charge stabilizing effect of α-chlorine is inferred to be greater than that of α-fluorine from reactivities in substitution reactions, this order could be reversed in the dissociated state because the electron-donating mesomeric effect of fluorine is greater than that of chlorine. The contribution from the halonium ion structure is also considered important only in the dissociated state.

(19) For example, the formation of CF_3CFClH from addition of HF to $CF_2{=}CFCl$ in SbF_5–SO_2 was explained in terms of the presumed greater stability of $^+CF_2CFClH$ as compared with that of HCF_2C^+FCl: G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **37**, 1028 (1972).

(20) G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Am. Chem. Soc.*, **94**, 3551 (1972). G. A. Olah, G. Liang, and Y. K. Mo, *J. Org. Chem.*, **39**, 2394 (1974).

(21) D. J. Burton and G. C. Briney, *J. Org. Chem.*, **35**, 3036 (1970).

(22) Isomerization of $CF_2ClCFCl_2$ by a continuous process using aluminum chloride packed in a column and "activated" with $CF_2ClCFCl_2$ is described: K. H. Hellberg and J. Massonne, *Chem. Ztg.*, **93**, 209 (1969).

(23) L. Pauling, "The Nature of the Chemical Bond", 3rd ed, Cornell University Press, Ithaca, N.Y., 1960, pp 71–72.

(24) A number of patents use aluminum fluoride, particularly in the form of fine particles, as catalyst for fluorination and disproportionation reactions. For example, J. D. Calfee and C. B. Miller, U.S. Patent 2 767 227 (1956); *Chem. Abstr.*, **51**, 7398h (1957).

(25) Stereoregular polymerization of methyl vinyl ether using aluminum fluoride is also reported: R. J. Kern and J. D. Calfee, *J. Polym. Sci., Part A-1*, **4**, 1609 (1966).

(26) For previous mechanistic discussions, see ref 4, 11a (pp 52–60), and 21.

(27) For such polychlorofluorinated systems it is not certain whether the structure of the intermediate cation (or cations) in the dissociated state is equilibrating carbonium ions or a halonium ion. Further, even if the intermediate exists mainly as a halonium ion, the reaction may occur only via carbonium ions. Hence, the carbonium ion structure is tentatively adopted.

(28) The alternative of direct transfer of fluoride is indirect transfer via a series of reversible reactions ($RF + AlX_3 \rightleftarrows R^+ + AlFX_3^-$). Though an unequivocal choice between direct transfer and indirect transfer is difficult at present, the direct transfer is preferred by the present author. In the gas phase reaction easy transfer, necessarily direct, of fluoride has recently been recognized: (a) N. A. McAskill, *Aust. J. Chem.*, **23**, 2301 (1970); (b) T. B. McMahon, R. J. Blint, D. P. Ridge, and J. L. Beauchamp, *J. Am. Chem. Soc.*, **94**, 8934 (1972); (c) R. J. Blint, T. B. McMahon, and J. L. Beauchamp, *ibid.*, **96**, 1269 (1974).

(29) Under the competitive conditions participation of the following reactions is undoubted if the above mechanisms are correct.

$$CF_2BrCF_2Br + {}^+CF_2CCl_3 \rightarrow CF_2BrC^+FBr + CF_3CCl_3$$

$$CF_2ClCFCl_2 + {}^+CF_2CFBr_2 \rightarrow CF_2ClC^+Cl_2 + CF_3CFBr_2$$

(30) The existence of fluoride acceptors stronger than aluminum chloride under isomerizing conditions is also indicated by the fact that the yield of CCl_3CCl_3 obtained from the reaction of $CF_2ClCFCl_2$ with aluminum chloride under isomerizing conditions is much higher than that obtained under nonisomerizing conditions. The main route of the formation of CCl_3CCl_3 from $CF_2ClCFCl_2$ under isomerizing conditions is considered to involve the conversion of CF_2ClCCl_3 into $CFCl_2CCl_3$ by intermolecular fluoride and chloride transfer.

(31) C. D. Nenitzescu, *Carbonium Ions*, **2**, 463–520 (1970).

(32) F. H. Field in "Ion-Molecule Reactions", Vol. 1, J. L. Franklin, Ed., Plenum Press, New York, N.Y., 1972, pp 265, 271, 274–275.

(33) A. L. Glasebrook and W. G. Lovell, *J. Am. Chem. Soc.*, **61**, 1717 (1939).

Reaction of an Unsymmetrical π Anion with Methylene Chloride/ *n*-Butyllithium. Preparation of Several $C_{18}H_{12}$ Hydrocarbons[1]

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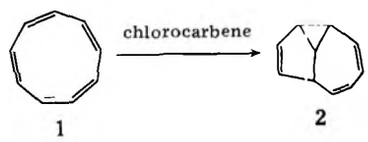
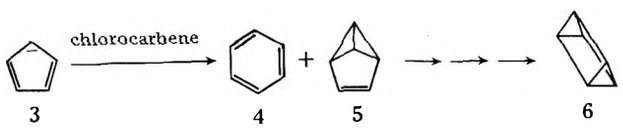
The reaction of the benz[*de*]anthracenyl anion (**17**) with methylene chloride/*n*-butyllithium is reported. The products of the reaction were shown to be 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**), 1,10-phenanthrotricyclo[4.1.0.0^{2,7}]heptene (**19**), and cyclohepta[*jk*]phenanthrene (**20**) in a ratio of 3:6:1, respectively; the overall yield was about 35%. The bicyclobutane **19** was converted into **20** and 1,10-phenanthrobicyclo[3.2.0]hepta-2,6-diene (**21**) by methods previously used for the bicyclobutane **11**. A qualitative scheme based on the total π-electron densities on the carbon atoms of **17** is used to rationalize the product distribution of the carbene reaction.

Ever since Katz and his co-workers prepared isobullvalene (**2**) by the reaction of the cyclononatetraenyl anion (**1**)



1 2

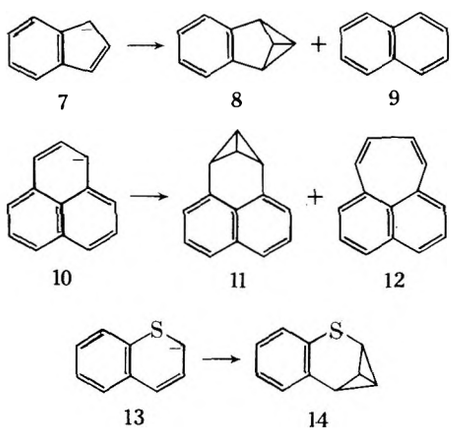
with methylene chloride and strong base,[3,4] the reaction of cyclic π anions with chlorocarbene[5] has received increasing attention,[6-9] because many interesting compounds can be made by this procedure that have proven difficult or impossible to make by more traditional approaches. Without doubt the most well-known compound that has been prepared by this procedure is benzvalene (**5**), it resulting from the reaction of the cyclopentadienyl anion (**3**) with CH_2Cl_2/CH_3Li.[6] An-



3 4 5 6

other notable feature of the chlorocarbene procedure is that many of the highly strained molecules produced in these reactions can be converted into other interesting compounds. Benzvalene (**5**), for example, has been converted into prismane (**6**),[10] a compound not known from any other route.

In a sense one can predict the products expected when the cyclic π anions, **1**,[3] **3**,[6] **7**,[6] **10**,[7,8] and **13**,[9] the ones which have been studied to date, are treated with methylene chloride and strong base. For the anions, **1**, **3**, and **10**, which possess high symmetry, there are a limited number of unique sites where the carbene can attack. For the anions, **7** and **13**, which lack high symmetry, there are still few plausible sites of attack for the carbene because the aromaticity of the anion would be destroyed in most of these attacks.

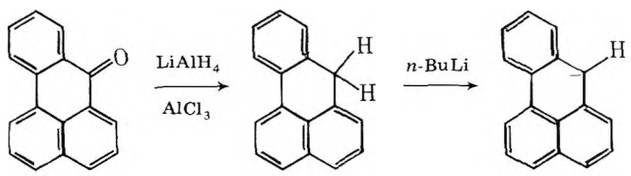


7 8 9

10 11 12

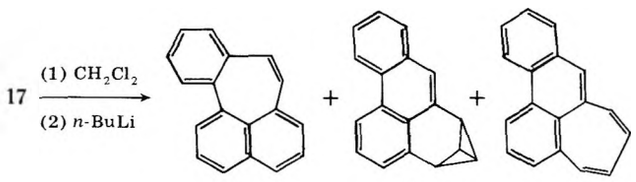
13 14

To make the reaction more useful it would be desirable to understand it in greater detail, thus transforming an intuitive approach to product prediction into a rational one. Although there are several ways one might do this, our initial endeavor was to look at an unsymmetrical anion where the carbene had several plausible points of attack. The benz[*de*]anthracenyl anion (**17**) was chosen because, in addition to fulfilling these criteria, it is easily prepared from the commercially available benzanthrone (**15**).[11]



15 16 17

The crude product resulting from the treatment of a solution of **17** in ether at dry ice–acetone temperature first with methylene chloride and then with *n*-butyllithium was shown to contain five products by thin layer chromatography. Three of these products, 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**), 1,10-phenanthrotricyclo[4.1.0.0^{2,7}]heptene (**19**), and cyclohepta[*jk*]phenanthrene (**20**), were formed in sufficient quantity to detect by NMR; two of these, **18** and **19**, could be separated by column chromatography on magnesium oxide[12,13] and isolated in sufficient quantity for spectral and analytical characterization.



18 19 20

NMR ratio 3 6 1

4,5-Benzocyclohepta[1,2,3-*de*]naphthalene (**18**), the minor of the two isolated products, consistently was formed in 10 to 12% yield. If one had an interest in preparing this nonbenzenoid aromatic hydrocarbon, the chlorocarbene route might not appear to be the synthetic method of choice. Considering the large number of steps which were required in previous syntheses of this compound,[14] however, this rapid two-step synthesis seems very attractive.

The major product formed in about 23% yield was shown to be the bicyclobutane **19**, first on the basis of its NMR spectrum (see Experimental Section) which is characteristic of phenanthrene derivatives[15] and then definitively by X-ray crystallography.[16]

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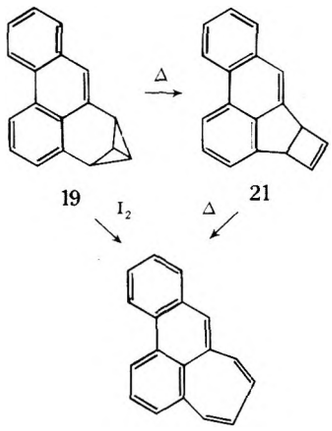
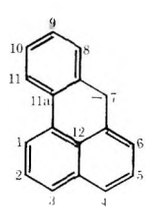
As was the case for the naphthobicyclobutane (**11**),[7,17] the phenanthrobicyclobutane (**19**) could be converted into isomeric hydrocarbons. Thermolysis, for example, led to the formation of 1,10-phenanthrobicyclo[3.2.0]hepta-2,6-diene (**21**), which, in turn, was converted into cyclohepta[*jk*]phenanthrene (**20**) on further heating. This latter compound could more conveniently be prepared by treating **19** with a catalytic amount of iodine. It should be noted that both **20** and **21** had not previously been reported in the literature.



20

Returning to the chlorocarbene reaction itself, can one explain the regioselectivity that has been observed? Note that **18** results from the attack of the carbene on C-7 of the anion **17**, while **19** and **20** result from the attack on C-4 and/or C-6. Qualitatively, one can indeed explain these results, although a quantitative treatment is not possible because the overall yield is far less than 100%. Shown below are the Hückel total π electron densities for the various carbons of **17**; C-7 has the largest value and C-4,6 have the next largest values. Thus, the electrophilic carbene has attacked the sites of highest electron density.



17

carbon[a]	total π electron density
7	1.247
4, 6	1.171
1, 3	1.110
8, 10, 11a	1.062
12	1.007

[a] Every other carbon has a value of 1.

The above analysis may seem surprising because π-electron densities are usually poor guides to regioselectivity in electrophilic reactions such as electrophilic aromatic substitution. The reaction of an electrophile such as a proton with an aromatic substrate to form a σ complex is normally endothermic, which means that the σ complex is a better model for the transition state than is the reactant aromatic substrate.

In the present case, the reaction of the electrophilic carbene with **17** may be exothermic, perhaps quite exothermic. If this is so, **17** should be a better model for the transition state than the resulting σ complex. In this event the π-electron densities at the various sites of **17** should reflect where the carbene will attack.

Even if this idea ultimately proves to be incorrect, at present it should be a useful guide in predicting where an unsymmetrical carbanion will be attacked by chlorocarbene.

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were recorded on Varian A-60 and HA-100 spectrometers, while mass spectra were recorded on a Perkin-Elmer RMU-6E spectrometer. Elemental analyses were performed by Galbraith Labs, Knoxville, Tenn.

Reaction of Benz[*de*]anthracenyl Anion with Methylene Chloride/*n*-Butyllithium. To a solution of 6.92 g (32.1 mmol) of 7*H*-benz[*de*]anthracene[11] in 1 L of ether was added under nitrogen 22.5 mL of 1.6 *M* *n*-butyllithium (36.0 mmol). After stirring the purple solution at room temperature for 1 h and then cooling in a dry ice–acetone bath, 5.0 mL of methylene chloride was added over 0.5 h followed by an additional 24.0 mL of 1.6 M *n*-butyllithium (38.0 mmol) over 0.75 h. The dark green solution was warmed to room temperature, washed with water, and dried. Removal of the ether in vacuo gave an orange oil whose NMR spectrum showed the presence of 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**), 1,10-phenanthrotricyclo[4.1.0.0^{2,7}]heptene (**19**), and a barely perceptible amount of cyclohepta[*jk*]phenanthrene (**20**). After passage of a small amount of this oil through a Celite column (eluting with ligroine), sufficient polymeric material is removed so that the product ratio could be determined; the values were 3:6:1 for the products **18**, **19**, and **20**, respectively.

Attempted Separation of Products on Alumina. The crude product was chromatographed on alumina (Fisher, 80–200 mesh), eluting first with ligroine and then with increasing amounts of ether in ligroine. The first component off the column weighed 73.0 mg (blue fluorescence, aromatic absorption in NMR) and was not characterized. The second component was a green oil (682 mg) and was characterized as 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**). The third component, an orange solid weighing 1.09 g, was shown by NMR to be an admixture of 50% of 1,10-phenanthrotricyclo[4.1.0.0^{2,7}]heptene (**19**) and 50% of cyclohepta[*jk*]phenanthrene (**20**).

Characterization of 4,5-Benzocyclohepta[1,2,3-*de*]naphthalene (18). After carefully rechromatographing the green oil (second component above), the compound was induced to crystallize. An analytically pure sample was obtained after three recrystallizations from ligroine–ether and sublimation (100 °C (0.5 mm)). This afforded a yellow solid having: mp 66.0–66.5 °C (lit. mp 65 °C,[14a] 64–65 °C[14b]); mass spectrum, *m/e* 228 (parent peak); NMR (CCl_4) δ 6.98–7.70 (m, 10 H, benzo- and naphthoaromatic), and 6.45 (s, 2 H, vinyl). Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.69; H, 5.18.

Separation of Products on Magnesium Oxide. A 3.5 × 75 cm column was prepared as follows. Approximately 40 mL of MgO, which had been dampened with ligroine, was added to the column and tamped down firmly. The process was repeated until the column was full. After saturating the column with ligroine, the crude product from the reaction of 5.93 g of 7*H*-benz[*de*]anthracene with methylene chloride/*n*-butyllithium was added to the top. The column, which was eluted with ligroine, was run in the usual manner except that air or nitrogen pressure (≤10 psi) was applied to the top, while a partial vacuum (~50 mm) was applied to the bottom. This insured an acceptable flow rate.

4,5-Benzocyclohepta[1,2,3-*de*]naphthalene (**18**) was collected until the NMR spectrum of the eluate showed bicyclobutane peaks. The column was continued until all the bicyclobutane had come off. The bicyclobutane fractions were combined and they partially crystallized on standing. After separating the crystals, the oily residue was rechromatographed on MgO and the entire process was repeated. A total of three columns was run and yielded 447 mg of 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**) and 1.47 g of a solid that was >80% bicyclobutane (**19**).

Characterization of 1,10-Phenanthrotricyclo[4.1.0.0^{2,7}]heptene (19). Repeated recrystallization from ligroine/methylene chloride of the enriched bicyclobutane sample above gave an analytically pure sample of **19** having: mp 99–100 °C; mass spectrum, parent peak at *m/e* 228; NMR (CCl_4) δ 8.28–8.72 (m, 2 H, H-4 and -5 of the phenanthrene ring), 7.18–7.95 (m, 6 H, remaining phenanthrene protons), 3.10–3.38 (two overlapping t, 2 H, bicyclobutane benzylic), and 2.45–2.58 (t, 2 H, remaining bicyclobutane protons, J = 3.0 Hz). Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.84; H, 5.27.

Cyclohepta[*jk*]phenanthrene (20). A solution consisting of 10 mg of I_2 and 1.37 g of a mixture containing 40% of 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**) and 60% of 1,10-phenanthrotricyclo[4.1.0.0^{2,7}]heptene (**19**) in 50 mL of CCl_4 was stirred at room temperature for 18 h. After washing with aqueous $Na_2S_2O_3$, the CCl_4 was

dried and removed in vacuo. NMR of the red oil showed that the bicyclobutane had all reacted and been converted into cyclohepta[*jk*]phenanthrene (**20**). The two components were easily separated on an alumina column. The red **20** (568 mg) was recrystallized twice from ligroine/ether and sublimed to give analytically pure material having: mp 107–108 °C; mass spectrum, parent peak at *m/e* 228; NMR (CCl_4) δ 8.00–8.33 (m, 2 H, H-4 and H-5 of phenanthrene ring), 6.67–7.48 (m, 6 H, remaining aromatic), 5.87–6.32 (m, 2 H, vinyl adjacent to aromatic), and 5.18–5.62 (m, 2 H, remaining vinyl). Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.58: H, 5.29.

1,10-Phenanthrobicyclo[3.2.0]hepta-2,6-diene (21). Two tubes, one containing 800 mg of a mixture of 80% 1,10-phenanthrotricyclo[4.1.0.$0^{2,7}$]heptene (**19**) and 20% 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**) in 500 mL of cyclohexane and the other containing 120 mg of the same mixture in 50 mL of cyclohexane, were sealed in vacuo and heated at 150 °C for 8 h. After removing the cyclohexane, the residue was chromatographed on alumina eluting with ligroine and increasing amounts of ether in ligroine. The first component (690 mg) off the column was a mixture of 1,10-phenanthrobicyclo[3.2.0]hepta-2,6-diene (**21**) (70%) and 4,5-benzocyclohepta[1,2,3-*de*]naphthalene (**18**) (30%). The second component (101 mg) was shown by NMR to be cyclohepta[*jk*]phenanthrene (**20**).

Trituration of component 1 with ligroine/ether induced crystallization. Four recrystallizations of this solid from ligroine/ether afforded analytically pure 1,10-phenanthrobicyclo[3.2.0]hepta-2,6-diene (**21**) having: mp 133 °C; mass spectrum, *m/e* 228 (parent peak); NMR (CCl_4) δ 8.17–8.70 (m, 2 H, H-4 and -5 of phenanthrene ring), 7.26–7.93 (m, 6 H, remaining aromatic), 6.30 (s, 2 H, vinyl), and 4.63 (s, 2 H, benzylic). Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.61; H, 5.27.

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Registry No.—**17**, 63264-00-6; **18**, 198-73-2; **19**, 63212-63-5; **20**, 199-85-9; **21**, 63241-09-8; 7*H*-benz[*de*]anthracene, 199-94-0; butyllithium, 109-72-8; methylene chloride, 75-09-2.

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Oxidative Cyclization of 2-Allylphenols by Palladium(II) Acetate. Changes in Product Distribution

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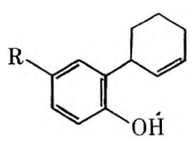
The cyclization of 2-allylphenols **1** having a cyclohexenyl moiety by an equimolar amount of $Pd(OAc)_2$ in air (MeOH, 25 °C) gives a mixture of *cis*-1,2,4a,9b- and *cis*-1,4,4a,9b-tetrahydrodibenzofurans **3** and **4** in nearly equal ratio, together with a small amount of 2,3-butanobenzofuran **5**. The addition of 9 equiv of cyclohexene to this reaction increases the proportion of **3** at the expense of those of **4** and **5**. Further, the distribution of these products changes with changing the substrate concentration. In the presence of excess substrate, the major product is again **3**. In the presence of O_2 (~1 atm), the cyclization proceeds catalytically with respect to Pd(II) without using another cooxidant such as Cu(II), and 0.5 molar equiv of O_2 is constantly consumed for the catalytic production of 1 mol of cyclized products (**3** + **4** + **5**). On the basis of these results, the observed change in product distribution is interpreted in terms of alternation of reacting Pd(II) species involved in the reactions and interaction of intermediate Pd(II) complexes with olefins. In relation to the stereochemistry of the intermediate oxypalladation adduct, the metal-exchange reaction of the trans oxymercurials I and II has been examined by using palladium(II) acetate.

The oxidative cyclization of 2-allylphenols by palladium(II) salts produces 2-substituted benzofurans or chromenes.[1,2] Cyclization of this type can be applicable to a variety of olefins bearing OH,[3] NOH,[4] COOH,[5] or NH_2[6] groups and provides a unique method for synthesizing heterocyclic compounds. The reaction is analogous to the oxidation of olefins by palladium(II),[7–9] and the isomer distribution of cyclized products is sensitively affected by small changes in the reaction conditions, the nature of ligands, and the structure of substrates. Thus, in the present study we have aimed to elucidate some of the fundamental factors controlling the distribution of isomeric benzofurans formed in the cyclization of 2-allylphenols by palladium(II) acetate. For this study, the allylphenols **1** and **2** (R = OMe or H) having cyclohexenyl and cyclopentenyl moieties were chosen since the product distri-



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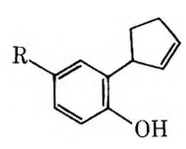

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a, R = OMe; **b**, R = H

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Table I. Product Distribution in the Cyclization of 1 and 2 with Palladium(II) Salts

Substrate	Palladium(II) salt	Yield, %	Product ratio[a]
1a	$Pd(OAc)_2$	73.3	46:49:5[e]
	$PdCl_2$–NaOAc (1:16)[b]	77.9	49:33:18[e]
1b	$Pd(OAc)_2$	86.0	39:56:5[e]
	$PdCl_2$–NaOAc (1:16)[b]	97.0	44:34:22[e]
2a	$Pd(OAc)_2$[c]	77.5	87:13:–[f]
2b	$Pd(OAc)_2$[c]	77.4	84:16:–[f]
	$PdCl_2$–NaOAc (1:16)[d]	46.4	80:20:–[f]

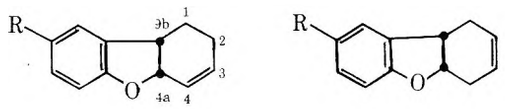
[a] The product ratio was determined by a combination of NMR and GLC analyses. [b] The reaction was carried out at 0 °C for 5 h. [c] The reaction was carried out at 55 °C for 3 h. [d] The reaction was carried out at 35 °C for 3 h. [e] Product ratio for **3**:**4**:**5**. [f] Product ratio for **6**:**7**:**8**.

butions from these substrates appeared to give an implication of the stereochemical process of this reaction.[1]

This paper mainly describes the following subjects: (i) the effect of substrate concentration on the isomer distribution; and (ii) elucidation of the catalytic process of this reaction.

Results

In this report, the product yields are all based on the palladium(II) salts used. The allylphenols **1** and **2** (**a**, R = OMe; **b**, R = H) were at first allowed to react with an equimolar amount of palladium(II) salt in MeOH–H_2O at 25 °C for 2 h in air. Results are given in Table I. Thus, the reaction of **1** (**a** or **b**) with $Pd(OAc)_2$ gives a mixture of **3** and **4** along with a small amount of the benzofuran **5**. The use of $PdCl_2$ alone as the reagent affords at least seven products,[10] but addition of NaOAc (16 equiv) to this reaction leads to only the three cyclized products **3**, **4**, and **5**. The cyclization of **2** (**a** or **b**) by $Pd(OAc)_2$ or $PdCl_2$–NaOAc (1:16) gives a mixture of **6** and **7**, but no benzofuran **8** corresponding to **5** is obtained at all.



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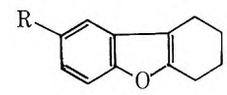

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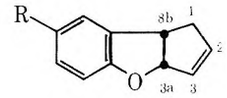

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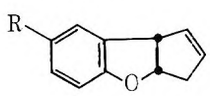

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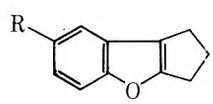

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a, R = OMe; b, R = H

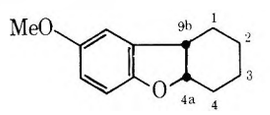
In the reactions using $Pd(OAc)_2$, no double-bond migration of the starting olefins was observed during the reactions. In addition, no secondary isomerization of the carbon–carbon double bonds in the products such as **3** → **5** occurred under the reaction conditions. However, the cyclized products **3** and **4** (**a** or **b**) underwent a small extent of disproportionation (vide infra).[11]

Hydrogenation of a mixture of **3a** and **4a** gives 1,2,3,4,4a,9b-hexahydro-8-methoxydibenzofuran (**9**) as the sole product. Similarly, a mixture of **6b** and **7b** affords 2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (**10**). Consequently, the products **3** and **4** or **6** and **7** are not stereoisomers between the C-4a and C-9b or C-3a and C-8b carbons, respectively. The stereochemistry of the fused furan ring at these carbons can be assigned as cis in all products since the NMR coupling constants of these protons (J = 7 ~ 8 Hz) are in agreement with reported values.[12] Table II, listing spectral and analytical data for these compounds, is given in the supplementary material.

Table III. Effect of Substrate Concentration on the Cyclization of 1a by Palladium(II) Acetate[a]

Run	Molar ratio 1a/$Pd(OAc)_2$	Cyclized products: Yield,[b] %	Cyclized products: Product ratio[c] 3a:4a:5a
1	0.5	34	37:57:6
2	1	73	46:49:5
3	2	176	56:40:4
4	5	254	66:32:2
5	10	606	74:24:2

[a] The reaction was carried out at 25 °C in MeOH–H_2O for 2 h in air. A 0.5-mmol amount of $Pd(OAc)_2$ was used in all runs. [b] Yields based on Pd(II) were determined by GLC using an internal standard. [c] Product ratios were determined by a combination of GLC and NMR analyses. The data are reproducible within ±1 ~ 2% by at least two separate experiments.



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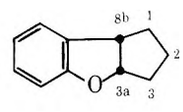

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All of the results described below are those derived from the reaction of **1a** (**a**, R = OMe) with $Pd(OAc)_2$. It is noted here that similar observations can be made by using **1b** (**b**, R = H). From Table III, firstly, it can be seen that the distribution of products **3a**–**5a** changes with changing the relative amount of substrate to $Pd(OAc)_2$ used. Thus, with increasing the concentration of **1a** relative to $Pd(OAc)_2$, the proportion of **3a** increases linearly at the expense of those of **4a** and **5a**. Furthermore, in the presence of excess **1a**, the reaction proceeds catalytically with respect to Pd(II). This result is remarkable in the regard that the catalytic reaction is effectively achieved without using another cooxidant such as Cu(II), which is required in most Pd(II)-catalyzed reactions of this type.[7a,13] For example, 0.5 mmol of $Pd(OAc)_2$ reacts with 5 mmol of **1a** to give 3.03 mmol of cyclized products; the catalytic turn-over is six times for Pd(II).[14] It should be noted here that the change observed in product distribution apparently correlates with the catalytic turn-over and that the proportion of **5a** is always extremely low.

When a nine-fold excess of cyclohexene, corresponding to the cyclohexenyl moiety of **1a**, was added to the 1:1 reaction, an 87% yield of cyclized products **3a**, **4a**, and **5a** was formed in a ratio of 70:21:9; the proportion of **3a** is evidently increased by this treatment (cf. run 2 in Table III). On the other hand, no significant effect was observed by a similar addition of *p*-methoxyphenol, corresponding to the phenolic moiety of **1a**. These results suggest that the predominant formation of **3a** in the presence of excess **1a** is due to an interaction between reactive Pd(II) species and the olefinic moiety of **1a**. The use of a highly coordinating solvent to Pd(II), such as acetonitrile, also resulted in the predominant formation of **3a**.

Under an atmosphere of nitrogen or argon, in place of air, no catalytic production of cyclized products was observed in the reaction of **1a**/$Pd(OAc)_2$ = 2. As shown in Table IV, the composition of products formed in this reaction changed with reaction time. Thus, the cyclized products **3a** and **4a** once formed were disproportionated into hexahydro-8-methoxydibenzofuran **9** and 8-methoxydibenzofuran (**11**), and the unreacted substrate **1a** was converted into a mixture of 2-

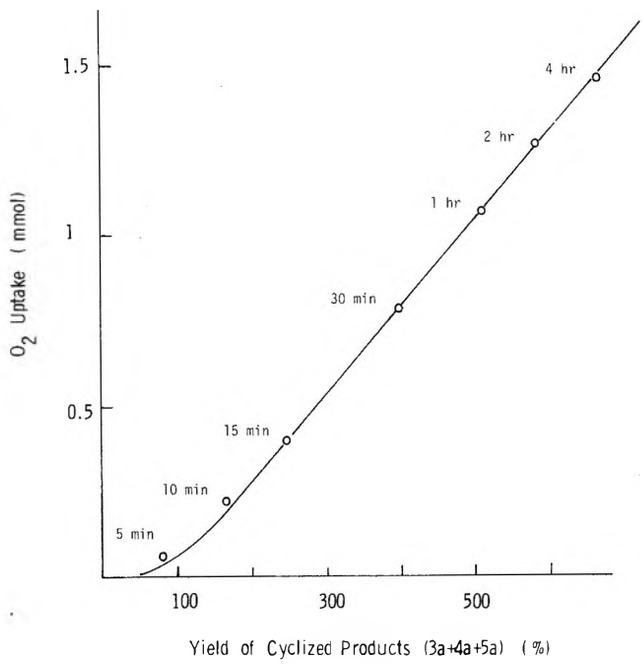


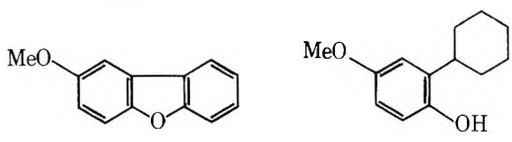
Figure 1. Plot of the O_2 uptake vs. the product yield of **3a** + **4a** + **5a** formed in the reaction of **1a** (5 mmol) and $Pd(OAc)_2$ (0.5 mmol) in MeOH-H_2O at 25 °C under an atmosphere of O_2 (~1 atm)

Table IV. Product Distribution in the Cyclization of 1a under Inert Atmospheres[a]

Reaction time, h	Unreacted 1a, %	Product yield,[b] % 3a + 4a	5a	9	11	12 + 13
0.5[c]	118	43	2		6	
2[c]			11	8	15	134
0.5[d]	115	36			7	
2[d]		3	10	8	15	106

[a] Reaction conditions: 1 mmol of **1a**, 0.5 mmol of $Pd(OAc)_2$, and 21 mL of MeOH-H_2O (18:3) at 25 °C under Ar or N_2. [b] Yields based on Pd(II) were determined by GLC using an internal standard. [c] Under Ar. [d] Under N_2.

cyclohexyl-4-methoxyphenol (**12**) and 2-phenyl-4-methoxyphenol (**13**). Therefore, the catalytic process of the foregoing reaction is evidently effected by atmospheric oxygen.



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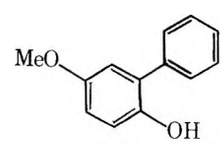

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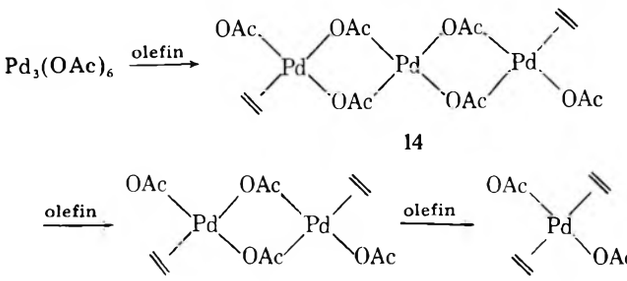
When the reaction of **1a**/$Pd(OAc)_2$ = 10 was performed under an atmosphere of oxygen (~1 atm), the oxygen uptake was found to correlate with the yield of cyclized products (Figure 1). Namely, 0.5 mmol of O_2 was constantly consumed for the production of 1 mmol of cyclized products (**3a** + **4a** + **5a**) formed in the region where the product yield is over 100%. When the reaction was carried out in anhydrous benzene, a stoichiometric amount of H_2O was detected from the reaction mixture by means of Karl Fischer titration. Therefore, the stoichiometry of the catalytic reaction can be represented as eq 1. When benzene was the solvent, a 736% yield of cyclized products was formed in a ratio of **3a**:**4a**:**5a** = 71:22:7. Again, the proportion of **5a** was quite low.

$$\mathbf{1a} + 0.5O_2 \rightarrow \mathbf{3a} + \mathbf{4a} + \mathbf{5a} + H_2O \quad (1)$$

Discussion

Since the distribution of products formed in a cyclization of this type has been found to be remarkably affected by the anionic ligand of palladium(II) salts,[2] our attention here has been directed to the reaction using palladium(II) acetate. Palladium(II) acetate as a solid is a trimeric ring structure bearing acetate bridges[15] which are necessarily cleaved in the initial stage of reaction. Since the cleavage is induced by the coordination of olefins or additives to the metal to give a trimeric, dimeric, and/or monomeric species such as **14**–**16**,[7,8,16] it is obvious that variations in the concentration of olefinic substrate give rise to changes in the degree of aggregation of palladium(II) acetate. Thus, in the presence of excess substrate, the substrate itself may act out the part of a ligand in reacting Pd(II) acetate. Accordingly, we propose that the observed dependence of product distribution on the substrate concentration (Table III) may be fundamentally ascribed to the different nature of reacting Pd(II) species involved in these reactions.[17]



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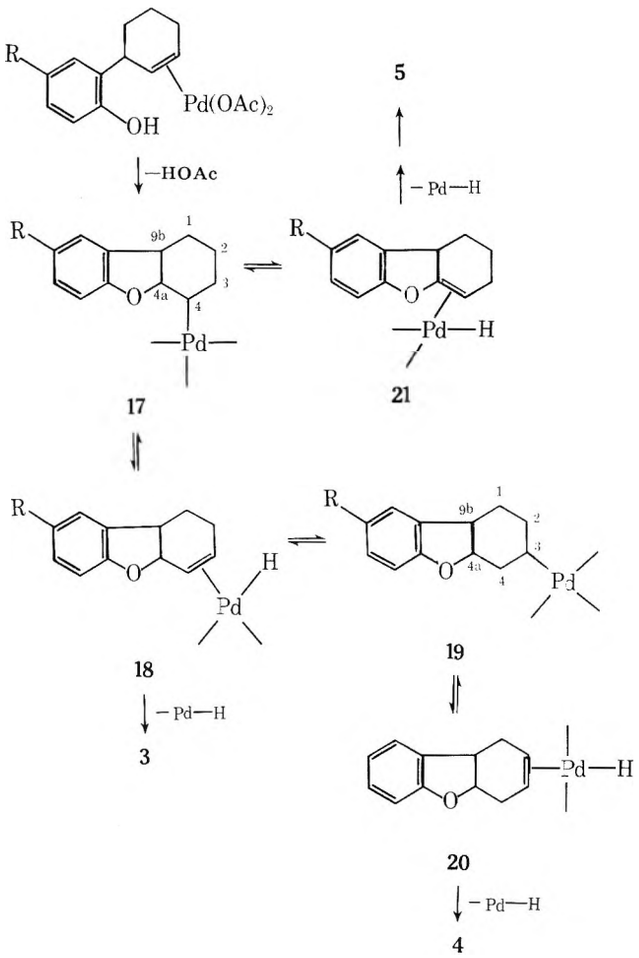
15 **16**

The product distribution itself can be rationalized in terms of intramolecular oxypalladation and palladium(II) hydride elimination–readditions, as shown in Scheme I. The first step in this reaction will proceed by intramolecular nucleophilic attack of the phenoxy group at the C=C bond of **1** coordinated to palladium(II) acetate. This process is accompanied by the loss of HOAc to give the oxypalladation adduct **17**. In the intermediate **17**, β palladium hydride elimination from the C-3 carbon produces the hydridopalladium olefin complex **18**. The complex **18** rearranges into the σ complex **19** by readdition of Pd–H in the opposite direction or gives product **3** with liberation of the Pd–H species. Hydride elimination from the C-2 carbon of **19** results in the formation of **4** via the hydridopalladium olefin complex **20**. The rearrangement of intermediate hydridopalladium olefin complexes, such as **18**, is most likely reversible in the coordination sphere of Pd(II)[18,19] The benzofuran **5** is formed from **21**, which is derived via β palladium hydride elimination from the C-4a carbon of **17**. The double-bond migration of **21** → **5** would, however, occur irreversibly since it gives rise to the thermodynamically more stable benzofuran **5**.

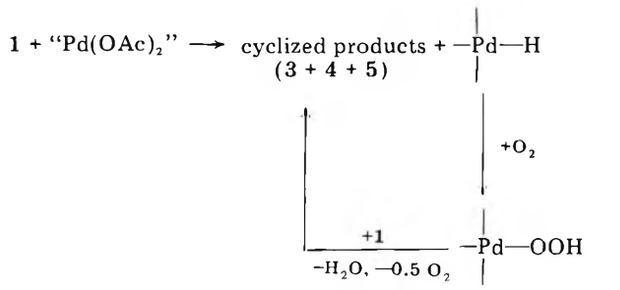
In view of all of this, the observed change in product distribution is ascribed to the change in equilibria among the intermediate complexes such as **17** ⇌ **18** ⇌ **19**. Thus, if the tetrahydrodibenzofuran **3** coordinated to Pd(II) in **18** is replaced by a free olefin such as the substrate itself or added cyclohexene, the proportion of **3** increases at the expense of those of **4** and **5**. Alternatively, it may simply be considered that the change in these equilibria is responsible for the difference in ligands of reactive Pd(II) species.[20]

The Pd–H species formed, whatever it is free or not, will

Scheme I

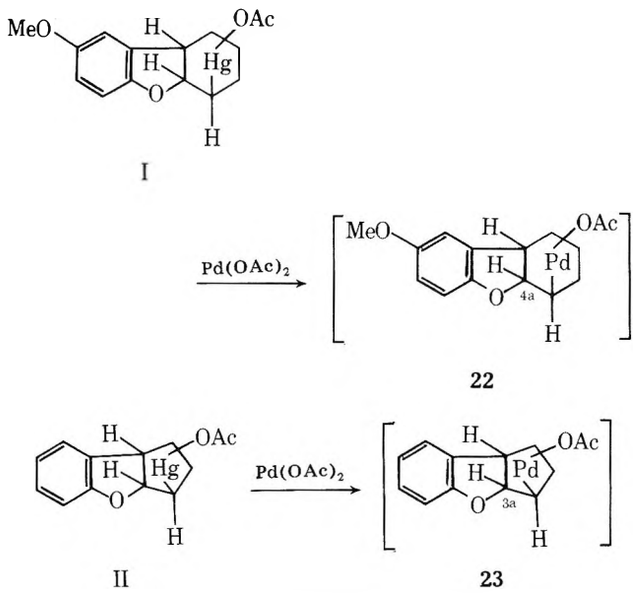


Scheme II



react with O_2, affording a hydroperoxypalladium(II) complex as a catalytic species. The existence of such a species is not unlikely since a rhodium hydride complex has been shown to react with O_2 to give a hydroperoxyrhodium complex.[21] The catalytic cycle given in Scheme II, wherein the ring closure of 1 proceeds by the loss of HOOH to give $0.5O_2$ and H_2O, is consistent with the observed stoichiometry of eq 1. Under the condition of an inert atmosphere, the Pd–H species decomposes to Pd(0), which could be active enough to catalyze the disproportionation of cyclohexenyl moieties of products and substrate.[22]

Finally, we will note here the stereochemistry of the oxypalladation adduct, which may be responsible for the formation of benzofuran **5** or **8**. Since the elimination of Pd–H generally occurs in a cis manner,[23] the trans oxypalladation adduct, e.g., **22** or **23**, is expected to give a relatively higher proportion of **5** or **8** via elimination of the cis hydrogen at the C-4a or C-3a carbons, respectively, but the cis adduct is not. When the trans adduct **22** was produced in situ by treating the trans oxymercurial I[24] with palladium(II) acetate in benzene



for 5 min,[25] a 27% combined yield of **3a, 4a,** and **5a** was formed in a ratio of 77:9:14. The proportion of **5a** was, however, not as high as we expected. The same treatment of *trans*-II afforded a 24% combined yield of **6b** and **7b** in a ratio of 90:10, but none of the expected benzofuran **8b** was formed at all. These results indicate that the hydride elimination from the C-4a or C-3a carbons does not occur with great facility, probably because it gives rise to an olefin of highly strained structure. Therefore, it can be said that a lower proportion of **5a** in the parent reaction is not necessarily dependent on the stereochemistry of the oxypalladation adduct.

Conclusion

The oxidative cyclization of 2-(2-cyclohexenyl)-4-methoxyphenol by palladium(II) acetate in the presence of O_2 is catalytic with respect to Pd(II) without using the usual carrier, Cu(II), which is required in most Pd(II)-catalyzed reactions of this type.[7a,13] Variations in the substrate concentration or the presence of cyclohexene change the product distribution observed. This may be responsible for the change in equilibria among intermediate complexes.

Experimental Section

NMR spectra were recorded on a 100-MHz Model JNM-4H-100 (JEOL) or a 60 MHz Model JNM-MH-60 (JEOL) spectrometer; chemical shifts (δ) are expressed in parts per million relative to Me_4Si. IR spectra were recorded on a Hitachi 215 spectrophotometer. Elemental analyses were performed by Mr. Y. Harada, Department of Chemistry, Faculty of Engineering Science, Osaka University. All temperatures were uncorrected.

Materials. Palladium(II) acetate was prepared by the following procedure. Palladium metal (>99.9% pure; 5.2 g) was dissolved in aqua regia (80 mL), and to this solution was added 40 mL of an aqueous solution of sodium formate (11.6 g). After the solution was heated at 80–90 °C for 5 min, pellets of sodium hydroxide (40 g) were slowly added at room temprature. The resulting palladium sponge was carefully washed with water by decantation until no Cl ion was detected by adding a few drops of $AgNO_3$ solution, and it was filtered with suction. After the palladium sponge was dried in vacuo, it was converted into palladium(II) acetate by nitric acid and glacial acetic acid according to the procedure of G. Wilkinson et al.[26] The glacial acetic acid, prepurified by $KMnO_4$ treatment,[8] was used for the preparation of pure palladium(II) acetate. The palladium(II) acetate of brown color was recrystallized from purified acetic acid containing a small amount of palladium sponge. The recrystallization was repeated two or three times. Palladium(II) chloride was prepared from a solution of palladium metal in aqua regia by repeated dilution with aqueous hydrogen chloride and heating to dryness. The allylphenols **1** and **2** (**a** or **b**) were synthesized by the Claisen rearrangement of the corresponding cycloalkenyl phenyl ethers.[27]

General Procedure for the Determination of Product Yield

and Its Distribution. The product ratio was determined by a combination of GLC and NMR analyses. The GLC analysis was performed on a JEOL flame ionization Model JGC-20KFP chromatograph using a 1 m × 4 mm, 10% PEG 20M Celite column under the conditions of injection temperature 250–300 °C and column temperature 110–250 °C. Since the isomeric tetrahydrodibenzofurans **3** and **4** (**a** or **b**) appear at the same retention time under the above conditions, the ratio of (**3** + **4**):**5** was first determined by GLC analysis and then the ratio of **3**:**4** was determined by NMR analysis. The determination of the ratio of **3a**:**4a** was performed by the measurment of peak areas of methoxy signals appearing at slightly different chemical shifts (**3a**, δ 3.68; **4a**, δ 3.67). In a similar way, the ratio of **3b**:**4b** was approximately determined by measuring peak areas of olefinic protons (**3b**, δ 5.90; **4b**, δ 5.78) simplified by a double irradiation technique. The product ratio of (**3a** + **4a**):**5a** was obtained at least three times by GLC analyses on each run and was reproducible within ±1% by at least two separate experiments. The ratios of **3a**:**4a** given in Table III are the average of five measurements by NMR spectroscopy from two separate experiments. Deviations from the average were ±2%.

For the determination of product yield by GLC, either biphenyl or naphthalene was chosen as an internal standard. The yield of **3** + **4** was determined by using the response factor of **3** (**a** or **b**) since the factor of a mixture of **3** and **4** was identical with that of purely isolated **3** (**a** or **b**).

At a final stage of this study, it was found that the products **3** and **4** (**a** or **b**) could be separated well by GLC using a 2 m × 4 mm, 15% silicon DC-QF-1 Celite column. The product ratio of **3a**:**4a** determined by the use of this column was nearly identical with that obtained by the NMR analysis (less than a 3% difference).

Isomerization of products during the process of GLC analysis of reaction mixtures did not occur.

General Procedure for Cyclization Using Palladium(II) Acetate. Palladium(II) acetate (0.112 g, 0.5 mmol) and an appropriate amount of internal standard for GLC analysis were placed in a 100-mL open flask containing a magnetic stirring bar, and a given amount of the substrate dissolved in methanol (18 mL) and water (3.3 mL) was added to the flask. The heterogeneous solution was stirred at 25 °C, and the reaction mixture was sequentially analyzed by GLC. After 2 h, the resulting palladium black was filtered off and the filtrate extracted with ether. The extract was washed with 10% aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. After the solvent was removed in vacuo, the residue was allowed to pass through a short column of alumina using pentane as the eluent. A mixture of cyclized products was obtained by distillation under reduced pressure. For the determination of the product ratio of **3**, **4**, and **5** (**a** or **b**), the distillate was subjected to GLC and NMR analyses. The results are given in Tables I and III. The boiling points of a mixture of cyclized products are as follows: **3a**, **4a**, and **5a**, 125–130 °C (6 mmHg); **3b**, **4b**, and **5b**, 82–86 °C (6 mmHg); **6a** and **7a**, 88–92 °C (4 mmHg); and **6b** and **7b**, 80–84 °C (6 mmHg). Isolation of pure products was performed by preparative GLC. The analytical and spectral data of the products are given in Table II (see supplementary material).

Check for Secondary Isomerization of Cyclized Products. In order to check secondary isomerization of the carbon–carbon double bond of products, blank experiments were carried out by using a mixture of isolated **3a** and **4a**. When a 67:33 mixture of **3a** and **4a** was treated with an equimolar amount of palladium(II) acetate in the presence or absence of a drop of acetic acid or palladium black, no formation of **5a** was observed and the ratio of **3a**:**4a** was invariant after 2 h. When the reaction of **1a** with an equimolar amount of palladium(II) acetate was followed by GLC, no significant change was observed in the GLC ratio of **3a**:**4a**:**5a**. In this case, the GLC analysis was performed using a 15% silicon DC-QF-1 Celite column. Similar observation was obtained in the reaction of **2b** with palladium(II) acetate.

Reaction of 1a with an Equimolar Amount of Palladium(II) Acetate in the Presence of Cyclohexene or *p*-Methoxyphenol. The allylphenol **1a** (0.102 g, 0.5 mmol) was allowed to react with palladium(II) acetate (0.112 g, 0.5 mmol) in the presence of cyclohexene (0.368 g, 4.5 mmol) for 2 h under the usual conditions. Analysis of the products showed that an 87% combined yield of **3a**, **4a**, and **5a** was formed in a ratio of 70:21:9.

The treatment of **1a** with palladium(II) acetate in the presence of *p*-methoxyphenol (9 equiv) gave a 75% combined yield of **3a**, **4a**, and **5a** in a ratio of 45:52:3.

Cyclization of 1 (a or b) and 2b by Palladium(II) Chloride in the Presence of Sodium Acetate. A suspended solution of palladium(II) chloride (0.5 mmol) and sodium acetate (8 mmol) in methanol (4 mL) and water (3.3 mL) was stirred at 0 °C for 5–10 min. Into the suspension was added **1** (0.5 mmol) and an internal standard dissolved in methanol (4 mL), and stirring was continued for 5 h at 0 °C. When the reaction temperature was 25 °C, the disproportionation of cyclized products **3**, **4**, and **5** predominantly occurred. Product yields and their distribution given in Table I were analyzed by the method described above.

The cyclization of **2b** was performed at 35 °C for 3 h under otherwise identical conditions.

Hydrogenation of a Mixture of Cyclized Products. A solution of a 56:44 mixture of **3a** and **4a** (0.150 g) in methanol (8 mL) was stirred in the presence of palladium on charcoal under a hydrogen atmosphere (~1 atm) at room temperature for 5 h. After the usual workup, 1,2,3,4,4a,9b-hexahydro-8-methoxydibenzofuran (**9**) was quantitatively obtained as a single product. Similarly, a 80:20 mixture of **6b** and **7b** gave 2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (**10**) as the sole product. The spectral and analytical data for **9** and **10** are listed in Table II.

Cyclization of 1a with Palladium(II) Acetate under an Atmosphere of Nitrogen or Argon. Palladium(II) acetate (0.112 g, 0.5 mmol) was placed in a 50-mL round-bottle flask equipped with a three-way stopcock and a magnetic stirring bar, and the flask was flushed with N_2 or Ar. A solution of **1a** (0.204 g, 1 mmol) and biphenyl (internal standard for GLC analysis) in methanol (18 mL) and water (3.3 mL) was introduced into the flask at room temperature, and stirring was continued for 2 h. An aliquot of the reaction mixture was periodically analyzed by GLC using a 10% PEG 20M Celite column (1 m × 4 mm). Peaks attributed to biphenyl (internal standard), **9**, **3a** + **4a**, **5a**, **11**, **1a**, and **12** + **13** appeared with retention times of 6, 14, 15, 16, 18, 24.5, and 25.5 min, respectively, under the conditions of injection temperature 250 °C and column temperature 170 °C, which was increased at the rate of 5, 10, and 5 °C/min after 6, 8, and 12 min, respectively. After the reaction was completed, the resulting palladium black was filtered off and the filtrate was extracted with 10% aqueous sodium hydroxide. From the ether extract, the cyclized products were obtained. The alkaline solution was acidified, and the phenolic products were extracted with ether. The ether solution was dried and distilled under reduced pressure. Isolation of products was performed by preparative GLC. However, the isolation of the phenolic products **12** and **13** in a pure form was unsuccessful because of very poor separation by GLC. A 62:38 mixture of **12** and **13**,[28] when isolated by preparative GLC, showed the following resonances in the NMR spectrum (60 MHz, CCl_4). **12:** δ 1.03–2.03 (m, 10 H), 2.53–3.05 (m, 1 H), 3.70 (s, 3 H, OCH_3), 5.36 (broad s, 1 H, OH), and 6.60 (m, 3 H, phenyl). **13:** δ 3.73 (s, 3 H, OCH_3), 5.55 (broad s, 1 H, OH), 6.76 (m, 3 H, phenyl), and 7.37 (m, 5 H, phenyl). These assignments were confirmed by comparison with the NMR spectrum of compound **12**, which was independently synthesized by the hydrogenation of **1a** with palladium on charcoal. Further, a 41:59 mixture of **12** and **13** was obtainable by heating the cyclohexylphenol **12** at 240 °C for 8 h in the presence of palladium on charcoal.[29]

The compound **11** isolated by preparative GLC showed the following data: IR (neat) 1600, 1482, 1450, 1437, 1318, 1295, 1225, 1185, 1163, 1100, 1028, 835, 800, 740, and 718 cm^{-1}; NMR (60 MHz) δ (CCl_4) 3.84 (s, 3 H) and 6.8–7.9 (m, 7 H).

Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.82; H, 5.09. Found: C, 78.51; H, 5.30.

The spectral and analytical data for other products are given in Table II.

Cyclization of 1a with Palladium(II) Acetate Under an Atmosphere of Oxygen. A 50-mL three-neck flask equipped with an addition tube for the solid palladium(II) acetate, a three-way stopcock with a serum cap, and a magnetic stirring bar was connected to a low-pressure hydrogenation apparatus filled with O_2. A solution of **1a** (1.020 g, 5 mmol) and biphenyl (internal standard for GLC analysis) in methanol (18 mL) and water (3.3 mL) was introduced into the reaction flask, and palladium(II) acetate (0.112 g, 0.5 mmol) was placed in the addition tube. The system was first evacuated with an aspirator from one side of the three-way stopcock and then flushed with O_2. After the procedure was repeated several times, the solid palladium(II) acetate was added to the solution at 25 °C by inverting the reaction flask, and the oxygen uptake was immediately measured. An aliquot of the reaction mixture was periodically taken out by a syringe from the top of the three-way stopcock and analyzed by GLC. The results are shown in Figure 1.

When the reaction was carried out in dry benzene (10 mL) under otherwise identical conditions, a stoichiometric amount of water was detected from the reaction mixture by means of a Yanagimoto Karl Fisher reagent titrator (Model KY-100, Yanagimoto Manufacturing Co., Ltd.).

Reaction of the Mercurials I and II with Palladium(II) Acetate. The mercurial I[24] (0.231 g, 0.5 mmol) was added to a solution of palladium(II) acetate (0.112 g, 0.5 mmol) in benzene (6 mL) at room temperature with stirring. After 5 min, GLC analysis of the reaction mixture showed that only the three products **3a, 4a,** and **5a** were formed in 27% combined yield. In prolonged reaction it was found that the reaction was accompanied by the production of 2-(2-cyclohexenyl)-4-methoxyphenol (**1a**). The product ratio of **3a**:**4a**:**5a**, determined by averaging four experiments, was 77:9:14.

The reaction of the mercurial II with palladium(II) acetate under the same conditions as above gave a mixture of **6b** and **7b** (24% combined yield) in a ratio of 90:10.

Acknowledgment. We wish to thank Mr. H. Ohkata for his assistance in the experimental work at the initial stage of this research. Thanks are also given to Mr. Terawaki for measuring NMR spectra.

Registry No.—**1a,** 64252-19-3; **1b,** 14003-77-1; **2a,** 61076-48-0; **2b,** 6627-83-4; **3a,** 66324-22-9; **3b,** 66324-24-1; **4a,** 66324-23-0; **4b,** 66324-25-2; **5a,** 7291-77-2; **5b,** 13130-19-3; **6a,** 66324-26-3; **6b,** 66324-28-5; **7a,** 66324-27-4; **7b,** 66324-29-6; **8a,** 7196-06-7; **9,** 66324-30-9; **10,** 14855-05-1; **11,** 20357-70-4; **12,** 16790-05-9; **13,** 13522-82-2; palladium(II) acetate, 3375-31-3.

Supplementary Material Available: A listing of analytical and spectral data for **3**–**7** (**a** or **b**), **9,** and **10** in Table II (4 pages). Ordering information is given on any current masthead page.

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Host–Guest Complexation. 9. Macrocyclic Polyethers and Sulfides Shaped by One Rigid Dinaphthyl Unit and Attached Arms. Synthesis and Survey of Complexing Abilities[1,2]

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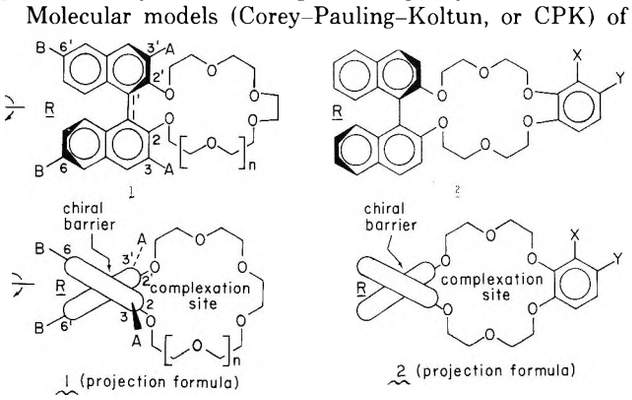
This paper reports the syntheses and characterization of a large number of stereoisomeric macrocyclic polyether and polyether–polythioether hosts that contain one 1,1′-dinaphthyl unit bound to oxygen or sulfur in the 2,2′-position. These macrocyclic compounds contain five to seven ring oxygens, or one to two sulfurs plus four to five ring oxygens. The ring heteroatoms are regularly spaced by their attachment to one another through 1,1′-dinaphthyl units, through ethylene, or through 1,2-benzene units. The heteroatoms, when turned inward, can become approximately coplanar. The naphthalene rings of the chiral 1,1′-dinaphthyl units occupy planes perpendicular to the plane of the macro ring, and these two aryls protrude from each face of the macro ring. The unshared electron pairs of the heteroatoms act as binding sites for appropriate metal or alkylammonium cations. Substituents attached at the 3,3′-positions of the 1,1′-dinaphthyl unit converge on and provide additional shape to the space surrounding the central binding hole of the macro ring. Certain of these units terminate in functional groups that provide additional ligands for cationic guests, in some cases supplying counterions for the charge on the guests. Substituents attached at the 6,6′-positions of the 1,1′-dinaphthyl unit diverge from the macro ring and its environment, and can be used to manipulate solubility properties or to bind the hosts to solid supports. Substituents attached at the 3- or 4-positions of the 1,2-benzene units, when long enough and in the proper conformations, can curl to place additional binding sites on the edge of the macro ring. The maximum rotations and absolute configurations of some of the optically active hosts were determined. Ring closures (6–65% yield) involved aryl oxide or aryl sulfide anion substitutions on appropriate alkyl ditosylates. Generalizations useful in developing synthetic strategies for these hosts are as follows. (1) Substituents in the 3-positions of the 1,1′-dinaphthyl unit had to be introduced before ring closure. (2) Alkyl, CH_2OH, and $CH_2N(CH_2CH_2)_2O$ substituents attached to the 3-positions of the naphthalene rings did not interfere with the ring-closing reactions. (3) Substituents in the 3- or 4-positions of the 1,2-benzene unit had to be introduced before ring closure. (4) Substituents attached to the 1,2-benzene unit that did not interfere with ring closures were $CH_2CH{=}CH_2$ in the 3-position and $(CH_2)_3OH$ in the 4-position. (5) Electrophilic substitution reactions of the macrocyclic ethers occurred in the 6-positions of the naphthalene rings and included bromination, acetylation, and chloromethylation. (6) Once introduced, substituents were subject to a wide variety of reactions that did not affect the configuration of the dinaphthyl or the integrity of the macrocyclic ring system. The complexing abilities of certain of the hosts toward Na^+, K^+, Ca^{2+}, Sr^{2+}, Ba^{2+}, $ArNH_3^+$, and RNH_3^+ were surveyed. In several cases in which the numbers of charges on host and guest matched, the salt complexes were characterized. The lipophilizing abilities of certain of the carboxylate-carrying hosts for Na^+, K^+, Ca^{2+}, and Ba^{2+} were compared. The complementary character of host–guest relationships is discussed.

Previous papers of this series described syntheses of macrocyclic host compounds containing one,[4,5] two,[5,6] or three[5] chiral 1,1′-dinaphthyl or 1,1′-ditetralyl[6] units. Ether oxygens were attached to the 2,2′-positions of these units and to ethylene, polyethyleneoxy,[4-6] 2,6-pyridinedimethylyl,[5] 2,5-tetrahydrofurandimethylyl,[5] or 1,3-benzenedimethyl units[5] to complete the macrocycles. The dinaphthyl or ditetralyl units act as chiral barriers, and the heteroatoms provide binding sites for alkylammonium or metal cationic guests in complexation. Paper 8 of this series describes the introduction of substituents into the 3,3′-positions of dilocular[5] cycles containing two dinaphthyl or ditetralyl units and into the 6,6′-positions of cycles containing two dinaphthyl units.[6]

Molecular models (Corey–Pauling–Koltun, or CPK) of hosts that contain one dinaphthyl unit and six ether oxygens, such as **1** (with $n = 1$) or **2**, indicate that, in their normal gauche conformations,[7] the six oxygens possess a roughly regular hexagonal arrangement. One of the naphthalene rings is above and in a plane tangent and perpendicular to the macro ring, and the other naphthalene ring is below and in a plane tangent and perpendicular to the macro ring. Thus the space not occupied by the naphthalene rings above and below each face of the macro ring is available for distribution of substituents a, b, and c of $abcCNH_3^+$ guest ions in complexes with these monolocular hosts. In contrast to the naphthalene rings in **2**, the benzene ring is roughly coplanar with the macro ring. Compounds **1**, when the two A groups are identical with one another and the two B groups are identical with one another, possess C_2 axes and are therefore "nonsided" (two faces of the macro ring are identical). Compounds **2**, when either substituents X or Y are other than H, are "sided", since these substituents destroy the C_2 axes of the structures.



1 (projection formula) **2** (projection formula)

Compounds represented by structure **1** are subject to variation in shapes with changes in the values of n which control hole size, and in the nature and bulk of substituents A attached to the 3-positions of the naphthalene rings. These substituents are located above and below the planes of the macro rings. When appropriately structured, substituents A can be used to place functional groups directly over and under the center of the hole of the macro ring to act as additional ligands for guests occupying that hole in the complexes. In

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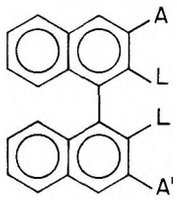
addition, these substituents can be used to further shape the chiral barrier. Because of their location with respect to the complexation site, substituents A are said to be convergent. In contrast, substituents B located in the 6-positions of the naphthalene rings diverge from the complexation site, and can be used to manipulate the solubility properties of the hosts or to attach them to solid supports. Although substituents X and Y in **2** diverge from the complexation site, when appropriately structured, they can potentially "return" to the edge of the complexation site to complex substituents a, b, and c of abcCNH$_3^+$ guests.

This paper reports on the syntheses and general survey of some of the complexing properties of compounds **1** and **2** with RNH$_3^+$, ArNH$_3^+$, M$^+$, and M^{2+} ions. Also reported are the syntheses of five cycles possessing the general structures of **1** and **2** with A = B = X = Y = H, but with some of the oxygens replaced with sulfur.

Results

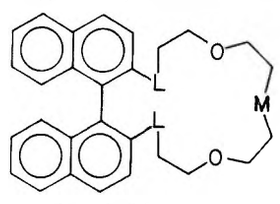
Syntheses. The following 1,1′-dinaphthyl compounds served as starting materials. Racemic and optically pure enantiomers of 2,2′-dihydroxy-1,1′-dinaphthyl (**3**) of known absolute configuration and optical stabilities have been previously reported,[5] as have racemic and optically pure enantiomers of the "dinaphthyl two-armed ditosylates"[5,6] (**4**). The two sulfhydryl units of 2,2′-disulfhydryl-1,1-dinaphthyl (**7**)



3, A=A′=H, L=OH
4, A=A′=H, L=O(CH$_2$CH$_2$O)$_2$Ts
5, A=A′=H, L=OCSN(CH$_3$)$_2$
6, A=A′=H, L=SCON(CH$_3$)$_2$
7, A=A′=H, L=SH
8, A=A′=CH$_2$OH, L=OH
9, A=CH$_2$OH, A′=H, L=OH
10, A=CH$_2$OH, A′=CH$_3$, L=OH
11, A=CH$_2$N(CH$_2$CH$_2$)$_2$O, A′=CH$_2$OH, L=OH
12, A=A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, L=OH
13, A=A′=CH$_2$N(CH$_3$)$_2$, L=OH

were introduced into the dinaphthyl system by a method patterned after that of Newman,[8] and involved the sequence **3** → **5** → **6** → **7**. The 280 °C required for the rearrangement of **5** → **6** undoubtedly would have led to racemic product had optically active starting material been used.[5] Compounds **8**, (*R*)-**8**, (*S*)-**8**, and **9–13** were available from previous studies[6].

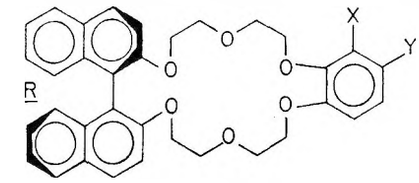
Macrocycles **14–18** which contained sulfur atoms as parts of their ring systems were synthesized as follows. Treatment of racemic dinaphthyl two-armed ditosylate **4** with disodium sulfide gave **14** (52%), with 1,2-ethanedithiol–NaOH gave **15**



14, L=O, M=S
15, L=O, M=SCH$_2$CH$_2$S
16, L=O, M=1,2-OC$_6$H$_4$O
17, L=O, M=1,2-OC$_6$H$_4$S
18, L=S, M=1,2-OC$_6$H$_4$O

(16%), with disulfhydrylbenzene–NaOH gave **16** (72%), and with 2-sulfhydrylphenol–KOH gave **17.** Dithiol **7** with KOH and 8,9-benzo-1,16-ditosyl-1,4,7,10,13,16-hexaoxahexadeca-8-ene[5] produced **18** (58%), which is isomeric to **16.**

The synthesis of parent host **19** with X = Y = H from ditosylate **4** and catechol was reported previously.[5] Similarly, from **4** and 3-allylcatechol–KOH,[9] a 41% yield of cycle was produced, 29% of which was **20** and 71% the corresponding allyl derivative (^{1}H NMR analysis). Accordingly, the mixture was treated with *t*-BuOH in benzene–*t*-BuOH, which completed the isomerization of the allyl to the propenyl group to produce an overall yield of 39% for **20.** This propenyl group



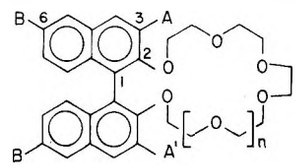
General Structure **2** (racemic)

19, X=Y=H
20, X= CH=CHCH$_3$, Y=H
21, X=H, Y=(CH$_2$)$_3$OH
22, X=CHO, Y=H
23, X=CH$_2$OH, Y=H
24, X=CH$_2$Cl, Y=H
25, X=CH$_2$N$_3$, Y=H
26, X=CH$_2$NHCOCH$_3$, Y=H
27, X=H, Y=(CH$_2$)$_3$Cl
28, X=H, Y=(CH$_2$)$_3$CO$_2$H

is a masked aldehyde group (see below), and provides an approach to attaching carbon substituents in the 3-position of the benzene ring of parent host **19.**

A route to compounds containing carbon substituents in the 4-position of the benzene ring of host **19** involves the readily available 3,4-dimethoxyallylbenzene[10] as starting material. Addition of diborane to this alkane, followed by oxidation of the adduct, gave 3-(3,4-dimethoxyphenyl)-1-propanol (84%) contaminated with 8.5% of 3-(3,4-dimethoxyphenyl)-2-propanol. The mixture was demethylated with BBr$_3$ to give 3-(3,4-dihydroxyphenyl)-1-propanol (78%) pure to TLC and ^{1}H NMR spectra (60% overall). When submitted to ring closure with ditosylate **4**–KOH, cycle **21** was obtained (46%). Thus the greater acidity of the phenolic hydroxyl groups over that of the alcohol group of the triol provides, with base, phenoxides in concentrations enough greater than alkoxide to direct the ring closure to the desired product **21.**

The side chains of cycles **20** and **21** were elaborated as follows. Controlled ozonolysis of alkene **20** gave aldehyde **22,** which was reduced (LiAlH$_4$) to alcohol **23** (80%, two steps). With thionyl chloride, **23** gave chloride **24** (~100%), which with NaN$_3$ gave azide **25** (80%). Reduction of **25** with LiAlH$_4$ gave the corresponding amine, acetylation of which produced



29, A=A′=CH$_2$OH, B=H, n=1
30, A=A′=CH$_2$OH, B=H, n=0
31, A=A′=CH$_2$OH, B=H, n=2
32, A=CH$_2$OH, A′=B=H, n=1
33, A=CH$_2$OH, A′=B=H, n=0
34, A=CH$_2$OH, A′=CH$_3$, B=H, n=1
35, A=CH$_2$N(CH$_2$CH$_2$)$_2$O, A′=CH$_2$OH, B=H, n=1
36, A=A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
37, A=A′=CH$_2$N(CH$_3$)$_2$, B=H, n=1
38, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=1
39, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=0
40, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=2
41, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=B=H, n=1
42, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=B=H, n=0
43, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
44, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=1
45, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=0
46, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=2
47, A=CH$_2$OCH$_2$CO$_2$H, A′=B=H, n=1
48, A=CH$_2$OCH$_2$CO$_2$H, A′=B=H, n=0
49, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_3$, B=H, n=1
50, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
51, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_2$OH, B=H, n=1
52, A=A′=CH$_2$Cl, B=H, n=1
53, A=A′=CH$_2$SCH$_2$CO$_2$H, B=H, n=1
54, A=A′=CH$_2$SCH$_2$CH$_2$CO$_2$H, B=H, n=1
55, A=A′=CH$_2$CH(CO$_2$H)$_2$, B=H, n=1
56, A=A′=CH$_2$CH$_2$CO$_2$H, B=H, n=1
57, A=A′=B=H, n=1
58, A=A′=H, B=Br, n=1
59, A=A′=H, B=COCH$_3$, n=1
60, A=A′=H, B=CH$_2$Cl, n=1
61, A=A′=B=CH$_2$Cl, n=1
62, A=A′=H, B=CO$_2$H, n=1
63, A=A′=H, B=CH$_2$OH, n=1
64, A=A′=B=CH$_2$OH, n=1
65, A=A′=H, B=CH$_2$OCH$_2$CO$_2$H, n=1
66, A=A′=H, B=CH$_2$SCH$_2$CO$_2$H, n=1
67, A=A′=B=CH$_2$SCH$_2$CO$_2$H, n=1

Table I. Abilities of Host Compounds in $CDCl_3$ to Dissolve by Complexation, Crystalline Salts of Alkylammonium, Arylammonium, Ammonium, and Hydronium Cations at Ambient Temperature

Host No.	Host Structure[a]	Salt structure	[Salt]/[host]
57[b]	$D(OEOEO)_2E$	t-$BuNH_3^+$ $(C_6H_5)_4B^-$	1.0
57[b]	$D(OEOEO)_2E$	$C_6H_5NH_3^+$ Cl^-	0.6
57[b]	$D(OEOEO)_2E$	$4\text{-}CH_3C_6H_4NH_3^+3,5\text{-}(NO_2)_2C_6H_3CO_2^-$	1.0
57[b]	$D(OEOEO)_2E$	$4\text{-}CH_3C_6H_4NH_3^+CHCl_2CO_2^-$	0.24
57[b]	$D(OEOEO)_2E$	$4\text{-}CH_3C_6H_4NH_3^+CCl_3CO_2^-$	1.3
57[b]	$D(OEOEO)_2E$	$4\text{-}BrC_6H_4NH_3^+Br^-$	1.3
57[b]	$D(OEOEO)_2E$	$4\text{-}CH_3OC_6H_4NH_3^+3,5\text{-}(NO_2)_2C_6H_3CO_2^-$	>1
57[b]	$D(OEOEO)_2E$	$C_6H_5CH(CH_3)NH_3^+3,5\text{-}(NO_2)_2C_6H_3CO_2^-$	0
57[b]	$D(OEOEO)_2E$	$C_6H_5CH(CH_3)NH_3^+2,4,6\text{-}(NO_2)_3C_6H_2O^-$	>0
57[b]	$D(OEOEO)_2E$	$NH_4^+CNS^-$	1.0
57[b]	$D(OEOEO)_2E$	$H_3O^+OTs^-$	1.0
68[b]	$D(OEOE)_2O$	t-$BuNH_3^+(C_6H_5)_4B^-$	1.0
19[c]	$D(OEOEO)_2T$	t-$BuNH_3^+(C_6H_5)_4B^-$	1.0
19[c]	$D(OEOEO)_2T$	$C_6H_5CH(CH_3)NH_3^+(C_6H_5)_4B^-$	1.5
19[c]	$D(OEOEO)_2T$	$NH_4^+SCN^-$	0.2
19[c]	$D(OEOEO)_2T$	$H_3O^+OTs^-$	1.0
26	$D(OEOEO)_2TCH_2NHAc$	t-$BuNH_3^+(C_6H_5)_4B^-$	1.0
28	$D(OEOEO)_2T(CH_2)_3CO_2H$	$NH_4^+SCN^-$	>0.2[d]
69[b]	$D(OEOEOH)_2$	t-$BuNH_3^+(C_6H_5)_4B^-$	0.3
70[e]	$D(OEOEO)_2D$	t-$BuNH_3^+(C_6H_5)_4B^-$	0.3
70[e]	$D(OEOEO)_2D$	$C_6H_5CH(CO_2CH_3)NH_3^+B(C_6H_5)_4^-$	0
70[e]	$D(OEOEO)_2D$	$C_6H_5CH(CH_3)NH_3^+2,4,6\text{-}(NO_2)_3C_6H_2O^-$	0
70[e]	$D(OEOEO)_2D$	$NH_4^+SCN^-$	0
47	$HO_2CCH_2OCH_2D(OEOEO)_2E$	t-$BuNH_3^+Br^-$	1.0
47	$HO_2CCH_2OCH_2D(OEOEO)_2E$	$C_6H_5NH_3^+Cl^-$	1.0

[a] D = 2,2′-disubstituted-1,1′-dinaphthyl, E = CH_2CH_2, T = 1,2-disubstituted benzene. [b] Reference 4. [c] Reference 5. [d] Spectral bands of host and guest overlap. [e] *(R,R)* isomer, ref 5.

amide **26** (57% based on azide). Alcohol **21** was converted with thionyl chloride to chloride **27** (95%), whose Grignard reagent with CO_2 gave carboxylic acid **28** (74%).

Macrocycles with substituents A and A′ attached at the 3-positions of the 1,1′-dinaphthyl unit were prepared by ring-closing reactions between tetra-, penta-, or hexaethylene glycol ditosylate[4,11] and optically pure enantiomers or racemates of tetrol **8**.[6] In THF–t-BuOK, the five-oxygen cycles **30** were formed in only 6–10% yield, but the six- and seven-oxygen cycles **29** and **31** were formed in 50–60% yields, respectively. Similarly, **9**–**13**[6] underwent ring-closing reactions with the appropriate ditosylates to give **32**–**37** in 31–64% yields. Thus CH_2OH, $CH_2N(CH_2CH_2)_2O$, and $CH_2N(CH_3)_2$ substituents in the 3,3′-positions of 2,2′-dihydroxy-1,1′-dinaphthyl (**1**) do not interfere with the ring closures.

The cycles containing CH_2OH groups in either the 3- or 3′- (or both) positions served as starting materials for side-chain elaboration. For example, **29** with NaH and $BrCH_2CO_2CH_3$ gave diester **38** in 60% yield. Similarly, (−)-(*S*)-**29** gave (−)-(*S*)-**38**, (−)-(*S*)-**30** gave (−)-(*S*)-**39**, **30** gave **39**, (−)-(*R*)-**31** gave (−)-(*R*)-**40**, **31** gave **40**, **32** gave **41**, **33** gave **42**, and **35** gave **43** (yields varied from 35 to 70%). Hydrolysis of these esters with barium hydroxide octahydrate in methanol gave, after acidification with hydrochloric acid, the corresponding acids (35–80%) (−)-(*S*)-**44**, **44**, (−)-(*S*)-**45**, **45**, (−)-(R)-**46**, **46**, **47**, **48**, **49**, and **50**. The use of less NaH and $BrCH_2CO_2CH_3$ with **29** and (+)-(*R*)-**29** led to the corresponding hydroxy esters, hydrolysis of which gave the respective hydroxy acids **51** (8% overall) and (+)-(*R*)-**51** (11% overall).

Treatment of diols **29** and (−)-(*S*)-**29** with thionyl chloride gave dichlorides **52** (91%) and (−)-(*S*)-**52** (81%), respectively. These arylmethyl chlorides reacted readily with thioglycolic or β-sulfhydrylpropionic acids to give diacids **53** (96%), (+)-(*S*)-**53** (72%), **54** (97%), and (−)-(*S*)-**54** (58%), respectively. With sodium dimethyl malonate, **52** gave tetraester, hydrolysis of which gave tetraacid **55** (59% overall). When heated, **55** decarboxylated to give diacid **56** (92%), which contains two propanoic acid side chains. Similarly, dichloride (−)-(*S*)-**52** gave (−)-(*S*)-**56** (37% overall).

Interestingly, the optical rotations of some of the carboxylic acids changed sign at λ 578 and 546 nm when the solvent was changed from THF to $CHCl_3$. This behavior was observed for (*S*)-**44**, (*R*)-**51**, (*S*)-**54**, and (*S*)-**56**.

Macrocycles with β substituents attached to the 6-positions of the 1,1′-dinaphthyl were prepared making use of the directing effects of the ether oxygens of parent host **57**[4] in the electrophilic substitution. When brominated in CH_2Cl_2 with Br_2 without catalyst, **57**[4] gave dibromide **58** (67%), whose structure was established by the splitting patterns of the aromatic protons in the ^1H NMR spectrum of the compound (see Experimental Section). With acetyl chloride–aluminum chloride in nitrobenzene, the 6,6′-diacetyl derivative **59** (36%) was produced. The structure of this compound was also established from its ^1H NMR spectrum. Chloromethylation of **57** with chloromethyl methyl ether in $CHCl_3$–$SnCl_4$ at −60 °C gave 6,6′-bis(chloromethyl) derivative **60** (50%). Likewise, chloromethylation of cycle **52** already containing two chloromethyl groups in the 3,3′-positions gave cycle **61** containing four chloromethyl groups in the 3-, 3′-, 6-, and 6′-positions. Spectral comparisons (^1H NMR) of **57**, **52**, **60**, and **61** established the positions of chloromethylation of **57** to give **60** and of **52** to give **61**.

Compounds **59**, **60**, and **61** served as starting materials for modification of the side chains in the 6- and 3-positions of the naphthalene rings. Oxidation of diacetyl cycle **59** with KOBr in THF gave diacid **62** (84%), reduction of which ($LiAlH_4$) produced diol **63** (74%). Tetrol **64** was produced by acetolysis of tetra(chloromethyl) cycle **61** to give the tetraacetate of **64** (76%), reduction of which ($LiAlH_4$) produced **64** (90%). With NaH–$BrCH_2CO_2CH_3$, diol **63** gave the dimethyl ester of diacid **65**, hydrolysis of which gave diacid **65** (41% overall). Bis(chloromethyl) cycle **60** with thioglycolic acid gave diacid **66** (75%), whereas tetra(chloromethyl) cycle **61** gave tetraacid **67** (96%).

Table II. Abilities of Host Compounds in $CDCl_3$ to Extract Alkylammonium Thiocyanate Salts from D_2O into $CDCl_3$ by Complexation at Ambient Temperature

Host No.	Host Structure[a]	Salt cation	[Salt]/[host][b]
57[c]	$D(OEOEO)_2E$	$C_6H_5CH(CH_3)NH_3^+$	2.0
57[c]	$D(OEOEO)_2E$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.8
19[d]	$D(OEOEO)_2T$	$C_6H_5CH(CH_3)NH_3^+$	1.9
19[d]	$D(OEOEO)_2T$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.7
28	$D(OEOEO)_2T(CH_2)_3CO_2H$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.8

[a] D = 2,2′-disubstituted-1,1′-dinaphthyl, E = CH_2CH_2, T = 1,2-disubstituted benzene. [b] ^1H NMR spectral criteria. [c] Reference 4. [d] Reference 5.

Survey of Abilities of Hosts to Complex Ammonium, Arylammonium, and Hydronium Salts. In the abbreviated formulas of the tables and following sections, D stands for the 1,1′-dinaphthyl unit bound to oxygen at its 2,2′-position, E stands for the 1,2-ethylene unit, and T stands for the benzene unit attached to oxygen at its 1,2-positions.

Through use of ^1H NMR integration techniques, hosts **57, 68, 19, 26, 28, 69, 70,** and **47** were examined for their abilities to enhance, by complexation, the solubilities of a variety of crystalline salts in $CDCl_3$ at ambient temperature. Direct evidence for complexation of the host was found in changes in chemical shifts of the naphthyl OCH_2 protons when salt was present. Table I reports the results.

A second study determined the capacity of hosts dissolved in $CDCl_3$ to extract, by complexation, alkylammonium salts from D_2O solution. Hosts **57, 19,** and **28** and guests $C_6H_5CH(CH_3)NH_3^+SCN^-$ and $C_6H_5CH(CO_2CH_3)NH_3^+SCN^-$ were examined. Table II reports the results.

The complexing of dilocular host **70** [$D(OEOEO)_2D$] with CH_3OD was also demonstrated by extraction. The high melting point and low solubility of (*RR*), (*S,S*)-**70** in CS_2 required that (*R,R*)-**70** be used. A solution of (*R,R*)-**70** in CS_2 was shaken at −78 °C with a 20% by volume solution of D_2O in CH_3OD which was 0.66 M in $LiPF_6$. The layers were carefully separated at −78 °C. The ^1H NMR spectrum of the organic layer at ambient temperature revealed the presence of equimolar quantities of host and CH_3OD. Repetition of the experiment in the absence of host gave no detectable CH_3OD. Thus, (*R,R*)-**70** complexes only 1 mol of CH_3OD in CS_2 at −78 °C.

Two crystalline 1:1 complexes of primary amine salts with hosts were prepared for determinations of their compositions and X-ray structures. The first involved the five-oxygen cycle **68** [$D(OEOE)_2O$] and *t*-$BuNH_3^+B(C_6H_5)_4^-$, and was obtained by mixing the components in $CDCl_3$. The second complex involved optically pure (*R*)-$C_6H_5CH(CO_2CH_3)NH_3^+PF_6^-$, which was extracted at −13 °C from a 4 M $LiPF_6$–D_2O solution into a $CDCl_3$ solution of optically pure (*S,S*)-**70**[5] [$D(OEOEO)_2D$]. Analysis showed the compound contained 1 mol of chloroform. The detailed X-ray structure of this compound is reported elsewhere.[12]

Several metal salts of hosts **50, 44, 45,** and **46** were prepared and examined. Amino ester **43** was hydrolyzed with KOH and the product was acidified with hydrochloric acid and extracted with $CHCl_3$. The extracted material when evaporated gave a powder whose mass spectrum gave a parent molecular ion at M^+ 713, but no peak at 675, the molecular weight of the parent amino acid **50.** Apparently the complex of **50** with KCl was extracted into $CHCl_3$, and HCl was lost when the complex was heated in the inlet tube of the mass spectrometer. The complex is, in effect, the hydrochloride of the amine and the potassium salt of the carboxylic acid. The potassium salt was made by neutralization of **50** with KOH and evaporation of the aqueous solution to give a powder.

Similar hydrolysis of amino ester **43** with $Ba(OH)_2$, acidification of the product with acetic acid, and extraction of the aqueous solution with $CHCl_3$ gave material that chromatographed on silica gel, 2:3 methanol–ether (v/v), to produce the barium salt of amino acid **50.** The analysis of this material indicated two ligand assemblies per barium ion. The ^1H NMR spectrum of the host portion of the salt was typical for complexed cycles, and was dramatically different from uncomplexed host **50.** The complex was slightly soluble in water and soluble in methanol, $CHCl_3$, and acetic acid. Thus the salt complex possesses mixed hydrophilic–lipophilic character. A solution of the complex in methanol–water was acidified with 5% sulfuric acid. No precipitate of $BaSO_4$ appeared.

The alkaline earth metal complexes of diacid **44** containing one dinaphthyl unit and six oxygens were prepared by hydrolyzing diester **38** with the appropriate $M(OH)_2$. The salts formed were extracted into $CHCl_3$, and the solutions were evaporated to give the salt complexes as powders. Their ^1H NMR spectra indicate the macrocycles are complexed. Application of the same procedure to the five-oxygen cyclic diester **39** with $Ca(OH)_2$ and to the seven-oxygen cyclic diester **40** with $Ba(OH)_2$ gave the corresponding salt complexes of diacids **45** and **46.**

Diester **38** was hydrolyzed with excess $Ba(OH)_2$ which was 0.8% in $Sr(OH)_2$. After washing with CH_2Cl_2, the aqueous solution was acidified with excess acetic acid and extracted with $CHCl_3$. The mass spectrum of the material extracted gave not only M^+ 664 for the host diacid **44,** but also M^+ for the strontium salt complex of **44.** No M^+ was observed for the barium salt complex of diacid **44.** Thus diacid **44** scavenged strontium ion from bulk barium ion, and the strontium salt complex was selectively extracted from an aqueous acetic acid solution.

The relative lipophilizing abilities of the anions of monoacid 6-ring oxygen host **47** and 5-ring oxygen host **48** for Na^+, K^+, Ca^{2+}, and Ba^{2+} were estimated as follows. The salt complexes of these two acids and four cations were prepared by neutralization, CH_2Cl_2 extraction procedures. Metal content determinations were made for the two Ca salts by atomic absorption, and for the two Na and two K salts by air–acetylene flame emission.[14] Unfortunately, the method could not be applied to the two Ba salts due to the low sensitivity for this element with the air–acetylene flame analysis. The salts were assumed to contain two cyclic ligands for each Ba^{2+} ion by analogy with the salt complex with **50.**

The salt complexes in CH_2Cl_2 exhibited a carbonyl-stretching frequency at only 1724 cm^{-1} for those derived from **48** (the free acid gave 1575 cm^{-1}), and at only 1724 cm^{-1} for those of **47** (the free acid gave 1580 cm^{-1}). The band frequencies of the salt complexes were essentially independent of which metal ion was complexed. The UV extinction coefficients of the eight salt complexes were determined in CH_2Cl_2 at their λ_{max} of 337, 324, 294, 286, and 276 nm. The ^1H NMR spectra of the salt complex solutions in $CDCl_3$ were dramatically different from those of the free acids **47** and **48.** For example, the $ArCH_2$ protons of **48** appear as a singlet at δ 4.99

Table III. Ability of Host Acids to Distinguish between Metal Ions in Lipophilization

Conditions	Host	Metal anion	Ratios of q_A (q'_A)
CH_2Cl_2, I	48	Ca^{2+}	8.0
	48	Ba^{2+}	4.9
	48	Na^+	3.6
	48	K^+	1.0
CH_2Cl_2, I	47	K^+	13
	47	Na^+	3.6
	47	Ca^{2+}	1.3
	47	Ba^{2+}	1.0
Toluene, II	48	Ca^{2+}	480
	48	Na^+	1.4
	48	K^+	1.0
Toluene, II	47	Ca^{2+}	43
	47	Na^+	1.5
	47	K^+	1.0
Toluene, III	48	Ca^{2+}	53
	48	Ba^{2+}	1.0
Toluene, III	47	Ca^{2+}	38
	47	Ba^{2+}	1.0

in the acid, but as a quartet in its Ba^{2+} salts. Additionally, the $ArOCH_2$ and OCH_2O proton bands are moved in the salts with respect to where they are in the free acids. Clearly, the conformational organizations of the ligands in the salt complexes are different from those in the free acids.

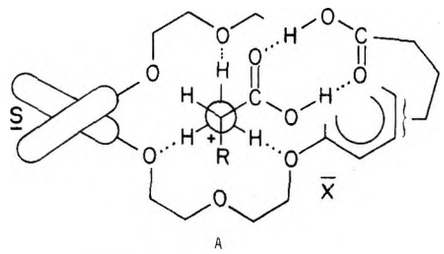
Distribution experiments were performed for the eight salt complexes between water–CH_2Cl_2 and water–toluene at 25 °C. Ultraviolet spectroscopy was used to determine the total ligand concentration in the organic and aqueous phases through the use of standards. The results were used to calculate for the four metal ions the ligand distribution ratios (q_A) between the two phases. The distribution ratio is defined as $q_A = 1a0_o/[A]_w$, where A is the anion of **47** or **48**, $[A]_o$ is the concentration of ligand in the organic solvent, and $[A]_w$ the concentration of ligand in water at equilibrium. The values of q_A vary with experimental conditions, and, therefore, comparisons of q_A values for the various salts are valid only when those values are obtained under the same conditions.[15] Comparisons of q_A as a lipophilization parameter for monovalent ions can be made directly. A semiquantitative comparison of values of this parameter between monovalent and divalent ions is provided by the assumption that $q'_A = q_A/2$, where q'_A applies to divalent ions and q_A values for monovalent ions are only compared with q'_A values for divalent ions, and when the experimental conditions for the extraction remain constant.

For the distribution experiments between water and CH_2Cl_2, all eight salt complexes were measured under one set of concentrations (water, 10^{-4} M in **47** or **48**, 10^{-2} M in NaOH, KOH, $Ca(OH)_2$, or $Ba(OH)_2$, 10^{-3} M in LiOH). In the experiments involving water–toluene, two sets of conditions were required because the range of lipophilization parameters was larger. The first set of conditions involved water, 2×10^{-3} M in **47** or **48**, 0.50 M in NaCl, KCl, or $CaCl_2$, 4.3×10^{-3} M in LiOH. The second set involved water 10^{-4} M in **47** or **48**, 0.95 M in $CaCl_2$ or $Ba(OH)_2$, and 10^{-3} M in LiOH. The LiOH was present to ensure that **47** and **48** were in the anionic form. Control experiments demonstrated that essentially no Li salt was extracted under the conditions used, and that the lithium salts present did not "salt out" the other salt complexes into the organic medium (see Experimental Section). In the tabulation of results, ratios of q_A (q'_A) values are listed for various combinations of the two different ligands, four different metal ions, and two different solvents. With CH_2Cl_2 as the organic solvent, all eight salt complexes could be distributed under the same conditions (conditions I). With toluene, two sets of concentrations had to be used (conditions II and III). Table III reports the results.

Discussion

Prior sections describe the syntheses of a large number of multiheteromacrocycles and determinations of their capacities to complex and lipophilize cations. Further studies will be described in future papers of this series.

Macrocycles **26** and **28** were prepared to test their abilities to act as hosts for complexing amino acids. With CPK models, amino acid salt complexes of **26** and **28** can be constructed in which the NH_3^+ group of the guest is bound to the ether oxygens of the host by hydrogen bonds, and the CO_2H group of the guest is hydrogen bonded to the $NHCOCH_3$ or the CO_2H group of the host. In the models of the complexes, either the R or the H group attached to the asymmetric center of the amino acid salt ($RCH^*(NH_3^+)CO_2H\ X^-$) is thrust into the chiral barrier (the binaphthyl group), depending on which diastereoisomeric complex is prepared. With amide **26** as host, the four stereoisomeric complexes that can be constructed using the two faces of the host do not provide a clear-cut prediction as to their stability order. In acid **28**, the arm carrying the CO_2H group is located almost on a C_2 axis of the host. Structure A represents the possible complexes between (*S*)-**28** and L-amino acid salts. These complexes are predicted



A

to be more stable than the corresponding diastereoisomeric complexes involving (*S*)-**28** and D-amino acid salts. The test of this prediction will involve the synthesis of the enantiomers of **28**. The synthesis of racemic **28** described in this paper indicates a feasible route to optically active **28**.

Abilities of Hosts to Complex by Hydrogen Bonding Ammonium, Alkylammonium, Arylammonium, and Hydronium Salts and Methanol. The results of Table I indicate that most of the cycles examined possessed the ability to solubilize in $CDCl_3$, NH_4^+, RNH_3^+, $ArNH_3^+$, and H_3O^+ salts in the crystalline state. Very likely, this lipophilization is due to complexation through a tripod arrangement of $^+NH\cdots O$ or $^+OH\cdots O$ hydrogen bonds, as has been found in several X-ray structures[12,16] and as is formulated in envisioned complex A.

All of the hosts tried complexed 1 mol of t-$BuNH_3^+$-$B(C_6H_5)_4^-$ except the open-chain model compound **69** [D(OEOEOH)$_2$][4] and the dilocular host **70** [D(OEOEO)$_2$D],[5] each of which complexed about 0.3 mol of salt. The lack of molecular organization of the host appears to reduce its complexing ability in the case of **69**. The lowered basicity of the four aryl oxygens of **70**, coupled with steric inhibition of complexation (CPK molecular model examination), are the factors that probably lower the binding power of **70**, as compared to **57**. Monolocular host **57** [D(OEOEO)$_2$E][4] complexed various para-substituted anilinium salts to give [salt]-/[host] ratios that varied from 0.24 to 1.3. With $NH_4^+SCN^-$ and $H_3O^+OTs^-$, **57** gave 1:1 complexes, whereas **19** [D(OEOEO)$_2$T][5] complexed only 0.2 mol of $NH_4^+SCN^-$ and dilocular host **70** complexed none. The lower basicity of the four ArO oxygens of **19** and **70** appear responsible for their lower complexing abilities of the NH_4^+ ion. The fact that **19** complexes 1.5 mol of $C_6H_5CH(CH_3)NH_3^+(C_6H_5)_4B^-$ provides a second example in which a host complexes more than one

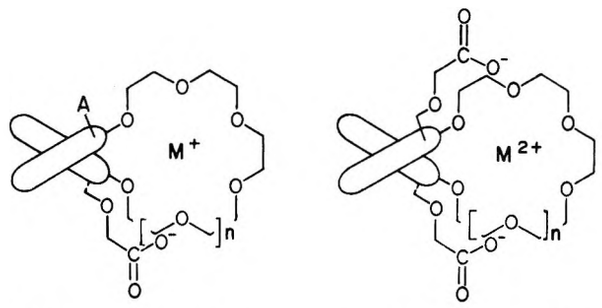
guest molecule. This might occur by one guest being bound to each face of the host, or by the complex involving only one or two hydrogen bonds between host and guest. The carboxyl-terminated arm of host **47** in the proper conformation can center the CO_2H group directly under the hole of the host (CPK molecular models), and this structural feature of the compound is probably responsible for **47** complexing 1 mol of $C_6H_5NH_3^+Cl^-$, as compared with the 0.6 mol complexed by the parent host **57.** The host whose carboxyl-terminated arm reaches only to the rim of the macrocycle (**28**) complexes $NH_4^+SCN^-$ somewhat better than its parent host **19.** The CO_2H group might provide a hydrogen bonding site for one end of the SCN^- ion, the other end being associated with the fourth N–H bond not hydrogen bonded to the host.

The results of Table II indicate that hosts **57, 19,** and **28** in $CDCl_3$ are able to extract $RNH_3^+SCN^-$ salts from water. Cycle D(OEOEO)$_2$E extracted 2.0 mol and **19** [(D(OEOEO)-$_2$T] about 1.9 mol of $C_6H_5CH(CH_3)NH_3^+SCN^-$, whereas their corresponding bromides were not extracted detectably. No detectable salt was extracted in the absence of host. The delocalization of negative charge in SCN^- and localization in Br^- suggests that more energy of solvation has to be overcome in transferring Br^- than SCN^- ion from D_2O into $CDCl_3$. Possibly 1 mol of guest cation is complexed at each face of the host. The less lipophilic salt, $C_6H_5CH(CO_2CH_3)NH_3^+$, was extracted to the extent of 0.8 mol by **57,** 0.7 mol by **19,** and 0.8 mol by **28,** which contains the carboxyl-terminated arm attached to the benzene ring. This arm appears to enhance the complexing ability of its host only to a small extent, possibly by hydrogen bonding the ester group. The structure envisioned resembles that of complex A.

The remarkable observation that (*R,R*)-**70** in CS_2 solution extracts at −78 °C from 80% CH_3OD–20% D_2O (by volume) only 1 mol of CH_3OD per mole of host is explained as follows. Molecular models (CPK) of a 1:1 complex can be constructed in which the CH_3OD group is hydrogen bonded to an inward-turned oxygen of (*R,R*)-**70,** which allows the CH_3 group to nicely occupy the space between the two naphthalene walls of the host. Another attractive explanation that is compatible with the structures of host and guest involves insertion of the $S{=}C^+$ portion of a $S{=}C^+{-}S^-{\cdots}DOCH_3$ species into the hole of (*R,R*)-**70** much as the N_2^+ part of ArN_2^- inserts into host compounds.[4]

Complexation and Lipophilization of Metal Ions. Molecular models (CPK) of hosts that contain $CH_2OCH_2CO_2H$ side chains substituted in the 3-positions of the naphthalene rings indicate that one oxygen of one carboxylate group can center directly under, and that of the second carboxylate, if present, directly over the hole of the macrocycle. When metal cations occupy that hole, the carboxylate anions are ideally positioned (both with respect to conformations and length of the side chain) to act as contact counterions for the complexed metals. Since the number of carboxylates and the sizes of the holes are subject to design, it seemed probable that hosts could be tailored to the valence and ligand preferences (number, type, and arrangement) of various metal cations.

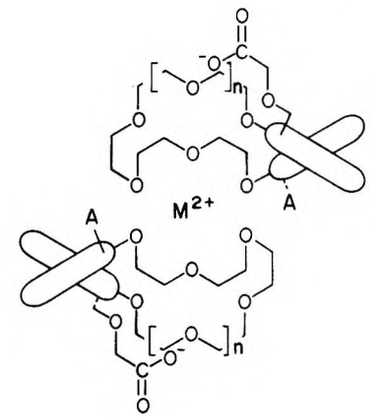
Three structures of differing charge type are envisioned as possible for the complexes. In **71–73,** the charge of a monovalent metal ion matches the charge of one carboxylate group of the host. In **74–78,** the charge of the divalent metal ion matches the charge of the two carboxylate groups of the host. In **79–81,** the charge of the divalent metal does not match the single carboxylate of the host, and thus two hosts per metal ion are required to balance the charge. The structures are drawn in such a way to maximize the number of metal ion to oxygen contacts, with the carboxylate and ether oxygens acting cooperatively. In the last type of complex, the number of contacts can be maximized only by sandwiching the metal ion between two macro rings, with an oxygen of a carboxylate



71, A=$CH_2N(CH_2CH_2)_2O$, M=K, n=1
72, A=H, M=K, n=0
73, A=H, M=Na, n=0

74, M=Ca, n=1
75, M=Sr, n=1
76, M=Ba, n=1

77, M=Ca, n=0
78, M=Ba, n=2



79, A=$CH_2N(CH_2CH_2)_2O$, M=Ba, n=1
80, A=H, M=Ca, n=1
81, A=H, M=Ba, n=1

82, A=H, M=Ca, n=0
83, A=H, M=Ba, n=0

occupying the center of each ring. Such an arrangement is compatible with CPK molecular models (coupled with appropriate spheres)[13] of **79, 81,** and **83** that involve Ba^+. In these structures, the metal ions are completely covered with a lipophilic skin of C–H bonds. However, Ca^{2+} is too small to contact both O^- groups at the same time when each O^- is centered in the middle of a five- or six-oxygen macro ring. Thus **80** and **82** are sterically incompatible structures. The structures for the two Ca^{2+} salt complexes which are sterically the most compatible involve six or seven oxygen–Ca contacts with one of the two ligands, and two oxygen–Ca contacts with the other (the labeled oxygens of the $CH_2\dot{O}CH_2C(=O)O^-$ group).

The interesting question arises as to how well the ionic diameters of the different metal cations match the holes of the different macro ring systems. To answer this question, graded ball bearings[13] were inserted into the centers of the holes of CPK molecular models of cycles containing five, six, or seven oxygens, with all the electron pairs of the oxygens turned inward, and all the OCH_2CH_2O units in gauche conformations. The diameters of those spheres that just contacted the oxygens of the macro ring with the O's coplanar are listed in Table IV for the minimum and maximum dihedral angles (θ) between the planes of the two naphthalene rings of the dinaphthyl unit. The minimum θ values place the two naphthyl oxygens as close together as do gauche oxygens of ethylene glycol. A second set of minimum diameters is also listed in which θ is minimized, the OCH_2CH_2O units are gauche, and the ring oxygens are as noncoplanar and staggered as possible. Table IV also contains the diameters of metal cations of interest here.

The hole diameters vary over a wide range of 1.7–4.0 Å, depending on the ring size (O's in ring), θ, and the staggering of the oxygens. With five ring oxygens, it can vary from 1.7 to 2.3 Å, and therefore the five-oxygen hosts might nicely accommodate Na^+ and Ca^{2+}, whose diameters are 1.90 and 1.98

Table IV. Comparisons of Hole Diameters of Hosts (All Gauche Conformations) with Ionic Diameters of Metals

No. of O's in ring of host	Hole diameter, Å: Minimum θ^a (~60°) O's coplanar	Minimum θ^a (~60°) O's staggered	Maximum θ, O's coplanar
5	1.9	1.7	2.3 (θ^a = 90°)
6	2.7	2.3	3.3 (θ^a = 95°)
7	3.2	2.8	4.0 (θ^a = 110°)

Guest	Ionic diameter, Å
Na^+	1.90
K^+	2.66
Ca^{2+}	1.98
Sr^{2+}	2.26
Ba^{2+}	2.70

[a] Dihedral angle between planes of two naphthalene rings.

Å, respectively. With six ring oxygens, it varies from 2.3 to 3.3 Å, and thus the six-oxygen hosts might nicely complex Sr^{2+}, K^+, and Ba^{2+}, whose diameters are 2.26, 2.66, and 2.70 Å, respectively. With seven ring oxygens, it varies from 2.8 to 4.0 Å, which is greater than the diameter of any of the ions, but is closest to Ba^{2+} (2.70 Å).

The qualitative results obtained with hosts **50** and **44–46** are interpreted in terms of the above structural parameters. The six ring oxygen host **50** containing one $CH_2OCH_2CO_2H$ and one $CH_2N(CH_2CH_2)_2O$ side chain formed particularly stable salt complexes with K^+ and Ba^{2+}. Structure **71** is probable for the salt complex formed from K^+ and **50.** The valences and diameters match, and the complex is stable enough to give a parent molecular ion at *m/e* 713 in its mass spectrum. Structure **79** is probable for the salt complex formed from Ba^{2+} and **50.** In this structure, the barium ion has 14 contact binding sites. The two O^- groups of the CH_2O-$CH_2CO_2^-$ arms protrude into the two holes of the macrocycles to contact the Ba^{2+}. The two sets of six ethers in their macro rings form "halos" opposite one another with Ba^{2+} in the center. This structure involves a minimum θ and hole diameter, and orientations of the oxygen's electron pairs toward the barium. Molecular models of **79** appear sterically compatible, although many conformations must be adjusted to have all ring oxygens contact Ba^{2+}. The Ba^{2+} is completely enveloped by the two ligand assemblies. The (*R*),(*S*) diastereoisomer that is formulated possesses a center of symmetry, but the racemate is equally likely. The stability of the complex to chromatography and to sulfuric acid is probably associated with the steric unavailability of Ba^{2+} to other ions or molecules of solvent.

The salt complexes of hosts **44–46** are presumed to have structures **74–78.** These structures are unique in the sense that the two carboxylate groups attached to the same molecule are separated by the macro ring and cannot converge and contact a divalent metal cation unless that metal is in the hole of the macro ring. The analysis of possible hole and metal ion diameters in Table IV suggests that all oxygens can contact all metal ions in structures **75, 76,** and **77,** but that the holes of **44** and **46** are too big for Ca^{2+} and Ba^{2+}, respectively.

The fact that **44** (six ring oxygens) scavenged trace amounts of Sr^{2+} from bulk Ba^{2+} indicates that complex **75** is more stable than **76.** The hole of **44** with $\theta \sim 60°$ can vary between 2.3 (O's staggered) and 2.7 Å (O's coplanar), whereas the diameters of Sr^{2+} and Ba^{2+} are 2.26 and 2.70 Å, respectively. These facts suggest that more stable salt complexes are formed when the oxygens are staggered than when coplanar. Models of **75** (the Sr^{2+} complex salt of **44**) indicate that the six ring oxygens must pucker maximally to contact the metal ion, and that they approach an octahedral arrangement. Thus the puckered all-gauche oxygen conformation in these salt complexes appears to be more stable than a coplanar, all-gauche oxygen arrangement. Attempts to grow crystals of these salt complexes suitable for X-ray structure determination failed.

The relative lipophilizing abilities of the anion of monoacid host **47** (six ring oxygens) and monoacid host **48** (five ring oxygens) for sodium, potassium, calcium, and barium cations (Table IV) are discussed in terms of structures **72, 73,** and **80–83.** As expected on basis of fits between host hole and guest diameters (Table IV), in CH_2Cl_2 the five ring oxygen ligand lipophilizes Na^+ more than K^+, and the six ring oxygen system lipophilizes K^+ more than Na^+. Surprisingly, the factor in each case was only about 4. In the same solvent, $Ca^{2+} \gtrsim Ba^{2+}$, in spite of the size changes in both host and guest. For the five ring oxygen ligand, Ca^{2+} or $Ba^{2+} \gtrsim Na^+$ or K^+, but for the six ring oxygen ligand, K^+ or $Na^+ > Ca^{2+}$ or Ba^{2+}.

In the less polar toluene solvent, the differences in lipophilizing abilities of the anions of the five and six ring oxygen ligands for Na^+ and K^+ becomes miniscule. However, in this solvent, Ca^{2+} is lipophilized 300–500 times more by the anion of the five-oxygen cycle, and 30 and 40 times more by the anion of the six-oxygen cycle than are Na^+ or K^+. Also, Ca^{2+} is lipophilized 50 times better by the five-oxygen cyclic anion and 40 times better by the six-oxygen cyclic anion than is Ba^{2+}. In other words, Ca^{2+} is lipophilized 1.5–2.5 powers of 10 better by the two cyclic ligands than by any of the other three ions.

The monovalent complexes probably possess a "nesting" type of structure typified by **72–73,** in which the metal ion is not far from being in the best plane of the surrounding ring oxygens. Possibly a mole of water is drawn into the organic phase to complete the coordination sphere of the metal ion on the side opposite the O^- group. The difference in energy cost of placing a molecule of water in this position in H_2O, CH_2Cl_2, and $C_6H_5CH_3$ solvents could be an important structural parameter that affects the changes in lipophilization of the Na^+ and K^+ ions.

Examinations of CPK molecular complexes of the sandwich type (**80–83**) provide more conclusions as to what structures are impossible than as to what structures probably exist. Barium ion is large enough for structures **81–83** to apply to the complex salts with the larger and smaller ring systems. Calcium ion is too small to contact both O^- groups and all 10 or 12 ring oxygens at the same time. Therefore, structures **80** and **82** cannot apply to the salt complexes of Ca^{2+}, and anion ligand and metal cation are not entirely complementary. The fact that Ca^{2+} is much more lipophilized than the other three ions in $C_6H_5CH_3$, but not in CH_2Cl_2, indicates that solvent polarity greatly affects the structures of the salt complex when host and guest are not entirely complementary. What is surprising is that the predicted complementary structural relationship between Ba^{2+} and its two ligand assemblies leads to lower lipophilization than the partially noncomplementary structural relationship between Ca^{2+} and its two ligand assemblies. A probably complicated and as yet nonunderstood set of superimposed effects must be responsible.

The important feature of these results is that Ca^{2+} is much more lipophilized by the anionic ligands in the solvent ($C_6H_5CH_3$) that most resembles cell membranes than are the Na^+ or K^+ ions. Thus the anion of **48** is a calcium selective ionophore of potentially important physiological significance.[17]

Experimental Section

General. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given in δ ppm from internal Me_4Si unless otherwise indicated, and were recorded on a Varian HA-100 or T-60 spectrometer. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter in a 1-dm ther-

mostatted cell. Infrared spectra were determined with a Beckman IR-5 spectrometer. Gel permeation chromatograms were run on a 3/8 in. × 20 ft column of styragel 100-Å beads in CH_2Cl_2(30–70 μm particle size, exclusion limit of 1500 molecular weight) at a flow rate of about 4 mL min^{-1} and a pressure of 200–400 psi. Mass spectra were taken at 70 EV on an AEI model MS-9 double-focusing spectrometer. All chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from CaH_2 prior to use. All reactions that involved KOH, KOBu-*t*, $LiAlH_4$, or NaH were conducted in an inert atmosphere of N_2 or Ar. Organic extracts were dried with $MgSO_4$. All noncrystalline macrocycles, once synthesized, were slightly air sensitive, and were therefore stored under Ar at 0 °C.

2,2′-Disulfhydryl-1,1′-dinaphthyl (7). To a stirred solution under N_2 of 60 g of diol **3** in 450 mL of dry DMF at 0 °C was added (2 h) 20.2 g of a 50% dispersion of NaH in mineral oil. To the resulting mixture was added 52 g of *N,N*-dimethylthiocarbamoyl chloride.[8] The stirred mixture was warmed over a 1-h period to 85 °C, and after 1 h at 85 °C the slurry was cooled and shaken with 1500 mL of 1% KOH in water. The solid that separated was collected, dried at 25 °C, and recrystallized from benzene–cyclohexane to give 83.5 g (86%) of 2,2′-bis(*N,N*-dimethylthiocarbamoyloxy)-1,1′-dinaphthyl (**5**): mp 208–209.5 °C; M^+ 260. Anal. Calcd for $C_{26}H_{24}O_2S_2N_2$: C, 67.79; H, 5.25. Found: C, 68.01; H, 5.07.

The above material, 75.3 g, was heated at 280 °C for 40 min. A high-boiling liquid refluxed. The metal was cooled, dissolved in 500 mL of $CHCl_3$, and chromatographed through a silica gel column. The column was washed with 4 L of $CHCl_3$, and the desired product eluted with 7 L of 1% methanol–99% $CHCl_3$. Evaporation of this eluate and crystallization and recrystallization of the residue from $CHCl_3$ gave 30.5 g (40%) of 2,2′-bis(*N,N*-dimethylcarbamoylthia)-1,1′-dinaphthyl (**6**): mp 245–247 °C; M^+ 460. Anal. Calcd for $C_{26}H_{24}O_2S_2N_2$: C, 67.79; H, 5.25. Found: C, 67.74; H, 5.24.

A slurry of 18.9 g of this material in 500 mL of methanol was refluxed under N_2 for 0.5 h. A 10% NaOH solution (100 mL, oxygen-free) was added (0.5 h), and the mixture was refluxed under N_2 for an additional 9 h, cooled, and concentrated. The solid produced was dissolved in 250 mL of oxygen-free water, washed with CH_2Cl_2, acidified carefully with 15 mL of concentrated H_2SO_4, crystallized, collected, and dried. This material was recrystallized twice from benzene to give 7.1 g (55%) of white **7**: mp 152.5–153.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 7.95–6.85 (m, ArH, 12), 3.2 (s, SH, 2). Anal. Calcd for $C_{20}H_{14}S_2$: C, 75.43; H, 4.43. Found: C, 75.38; H, 4.31.

3-Hydroxymethyl-2,2′-dihydroxy-1,1′-dinaphthyl (9). This synthesis is superior to that reported previously.[6] A solution of 50 g of 2,2′-dihydroxy-1,1-dinaphthyl (**3**) in 210 mL of $(C_2H_5OCH_2CH_2)_2O$ and 125 g of *N*-butoxymethylmorpholine[6] was heated and stirred under N_2 at 165 °C for 72 h. The solution was cooled and the solvent was evaporated at 0.1 mm. The residue was mixed with 300 mL of CH_2Cl_2 and 100 g of silica gel and the CH_2Cl_2 was evaporated at 30 mm and added as a slurry in 30% pentane in CH_2Cl_2 (by volume) to the top of a 300-g silica gel column. The product was eluted with the same solvent (6 L), the solvent was evaporated, and the residue was dissolved in 400 mL of CH_2Cl_2. The solution was stirred with 100 mL of 20% HCl in water for 1 h, and the hydrochloride of 3-morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl (separated) was collected and washed with 280 mL of CH_2Cl_2. The unreacted **3** remained in CH_2Cl_2 and the dihydrochloride of 3,3′-dimorpholino-2,2′-dihydroxy-1,1′-dinaphthyl (**12**)[6] remained in the aqueous phase. The desired monosubstituted salt was shaken with 500 mL of saturated $NaHCO_3$–H_2O solution and 100 mL of CH_2Cl_2. The aqueous layer was extracted with two additional 100-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated and the product was crystallized: mp 226–228 °C; wt 17.5 g or 54% based on unrecovered starting material. From the aqueous layer 21 g of **3** was recovered. The monomorpholino material (21 g) was heated at reflux under N_2 in 470 mL of Ac_2O for 8 days, and the solvent was distilled under reduced pressure. The residue was dried at 100 °C under 0.1 mm of pressure to give 23 g (95%) of 3-acetoxymethyl-2,2′-diacetoxy-1,1′-dinaphthyl. This material (23 g) in 400 mL of dry THF was added dropwise to 13 g of $LiAlH_4$ in dry ether under N_2, and the product, 3-hydroxymethyl-2,2′-dihydroxy-1,1′-dinaphthyl (**9**) was isolated in the usual way: wt 15 g (92%); mp 206–207 °C.[6]

2,3:4,5-Di(1,2-naphtho)-1,6,9,15-tetraoxa-12-thiacyclohexadeca-2,4-diene (14). A solution of 1.25 g of racemic dinaphthyl two-armed ditosylate[5] (**4**) in 400 mL of butanol and 40 mL of dioxane was stirred under N_2 at reflux, and 0.391 g of disodium sulfide nonahydrate in 15 mL of distilled water and 100 mL of butanol was added. The mixture was refluxed under N_2 for 17 h and concentrated under reduced pressure and the residue was triturated with $CHCl_3$. The mixture was filtered and the filtrate was evaporated and chromatographed on 200 g of silica gel. Product was eluted in fractions 10–14 of 100 mL each of 2% ethyl acetate–98% $CHCl_3$ (by volume) to give after recrystallization from methanol 0.386 g (52%) of **14**: mp 125–127 °C. A recrystallized sample gave: mp 127–128 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 8.0–7.7 (m, Ar, 4), 7.5–7.0 (m, ArH, 8), 4.5–3.8 (m, $ArOCH_2$, 4), 3.8–3.3 (m, ROCH, 8), 3.0–2.1 (m, SCH_2, 4), M^+ 460. Anal. Calcd for $C_{28}H_{28}O_4S$: C, 73.01; H, 6.13. Found: C, 72.97; H, 5.98.

2,3:4,5-Di(1,2-naphtho)-1,6,9,18-tetraoxa-12,15-dithiacycloeicosa-2,4-diene (15). To a solution of dinaphthyl two-armed ditosylate[5] (**4**; 10.0 g) and 1,2-ethanedithiol (1.22 g) in 800 mL of THF under N_2 was added 1.04 g of NaOH in 10 mL of water. The mixture was refluxed for 40 h, concentrated to 200 mL, and partitioned between 500 mL of CH_2Cl_2 and 600 mL of water. The layers were separated and the aqueous phase was extracted with two 200-mL portions of CH_2Cl_2. The combined organic phases were dried and evaporated and the residue was chromatographed on 150 g of basic alumina. The column was washed with benzene (2 L), 49:1 benzene–ether, 48:2 benzene–ether and 19:1 benzene–ether (v/v, 2 L each), and 9:1 benzene–ether (v/v, 3 L) to give 1.05 g (16%) of **15** in the final eluate, mp 85–90 °C. Recrystallization of this material gave: mp 85–90 °C; M^+ 520; ^1H NMR (60 MHz, $CDCl_3$) δ 7.96–7.00 (m, ArH, 12) and 4.30–2.30 (m, OCH_2, SCH_2, 20). Anal. Calcd for $C_{30}H_{32}O_4S_2$: C, 69.22; H, 6.20. Found: C, 69.01; H, 6.12.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-1,6,9,18-tetraoxa-12,15-dithiacycloeicosa-2,4,13-triene (16). The substance 1,2-disulfhydrylbenzene (0.1676 g) in 80 mL of butanol was stirred under N_2 for 0.5 h and 0.0965 g of NaOH pellets was added. Water was azeotropically distilled from the refluxing solution and then 0.9078 g of dinaphthyl two-armed ditosylate[5] (**4**) in 30 mL of N_2-flushed dioxane (purified) was added. The resulting slurry was stirred at reflux for 11 h. The reaction mixture was cooled and filtered and the solid washed well with $CHCl_3$ to give 0.356 g of NaOTs. The filtrate was concentrated under reduced pressure and the residual oil was chromatographed on 150 g of silica gel. Elution of column with $CHCl_3$ gave 0.618 g of crude product in fractions 7–12 (125 mL each), recrystallization of which from acetone twice gave 0.484 g (72%) of **16**: mp 149.5–151 °C; M^+ 568; ^1H NMR (60 MHz, $CDCl_3$) δ 7.9–7.6 (m, 4, ArH), 7.4–6.9 (m, 12, ArH), 4.1–3.7 (m, 4, $ArOCH_2$), 3.5–3.2 (m, 8, CH_2OCH_2), 3.0–2.7 (m, 4, $ArSCH_2$). Anal. Calcd for $C_{34}H_{32}O_4S_2$: C, 71.79; H, 5.67. Found: C, 72.00; H, 5.53.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-1,6,9,12,18-pentoxa-15-thiacycloeicosa-2,4,13-triene (17). The substance 2-sulfhydrylphenol (1.26 g) was stirred under N_2 in 1 L of THF and 2.24 g of *t*-BuOK and 30 mL of H_2O were added at reflux, followed by a solution of 7.70 g of dinaphthyl two-armed ditosylate[5] (**4**) in 300 mL of N_2-flushed THF and 60 mL of H_2O. The reaction mixture was held at reflux for 48 h and an additional 0.504 g of 2-sulfhydrylphenol and 0.88 g of 85% KOH were added. After refluxing for 24 h, the solution was evaporated under reduced pressure. The residue was slurried in $CHCl_3$ and filtered and the solid was washed with $CHCl_3$ to give 3.87 g (99%) of KOTs. The filtrate was washed with 5% NaOH solution, water, and brine, dried, and evaporated. The white paste was chromatographed on activity grade III dry-pack silica gel (775 g) in 0.5% EtOAc–99.5% $CHCl_3$ (by volume). After development of the 75-cm column with 2.4 L of the same solvent mixture, the column was sectioned and the product eluted in that part 6–26 cm from the bottom with 70% $CHCl_3$–30% CH_3OH (by volume). This material (2.26 g) was crystallized (slowly) from 160 mL of absolute ethanol to give 2.053 g (38%) of **17**, mp 106–113 °C, whose ^1H NMR spectrum was identical with that of an analytical sample: mp 111–113 °C. This material gave: M^+ 552; ^1H NMR (60 MHz, $CDCl_3$) δ 8.0–6.68 (m, 16, ArH), 4.2–3.86 (m, 6, $ArOCH_2$), 3.75–3.2 (m, 8, CH_2OCH_2), 3.2–2.5 (m, 2, $ArSCH_2$). Anal. Calcd for $C_{34}H_{32}O_5S$: C, 73.88; H, 5.84. Found: C, 73.93; H, 5.86.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-9,12,15,18-tetraoxa-1,6-dithiacycloeicosa-2,4,13-triene (18). To a solution 1.0 g of 2,2′-disulfhydryl-1,1′-dinaphthyl (**7**) and 0.434 g of KOH in 40 mL of H_2O stirred under N_2 was added (in 200 mL of THF and 28 mL of purified dioxane) 1.86 g of 8:9-benzo-1,16-ditosyl-1,4,7,10-13,16-hexaoxahexadeca-8-ene[5]. The resulting solution had a pH 7–8, which decreased to 5–6 after refluxing for 15 h. The solution was evaporated under reduced pressure and the residue was mixed with 50 mL of CH_2Cl_2 and filtered. The KOTs that separated was collected and washed with CH_2Cl_2 to give 0.903 g (69%) of salt. The filtrate was washed with 10% KOH in water and water and brine, dried, and evaporated under reduced pressure. The residue was crystallized from benzene and recrystallized from 50% benzene–50% cyclohexane (v/v) to give 1.14 g of **18** as a solvate, mp 154–155 °C, which after drying at 81 °C and 50 μm for 24 h gave 1.10 g (58%) of **18**: mp 167–168 °C; M^+

568; 111 NMR spectrum (60 MHz, $CDCl_3$) δ 8.1–6.9 (m, naphtho-H, 12), 6.85 (s, benzo-H, 4), 4.2–3.9 (m, $ArOCH_2$, 4), 3.9–3.6 (m, CH_2OCH_2, 8), 3.3–2.9 (m, $ArSCH_2$, 4). Anal. Calcd for $C_{34}H_{32}O_4S_2$: C, 71.79; H, 5.67. Found: C, 71.65; H, 5.85.

2,3:4,5-Dinaphtho-13,14-(3-propenyl-1,2-benzo)-1,6,9,12,15,-18-hexaoxacycloeicosa-2,4,13-triene (20). Procedure 1. A solution of 38.3 g of dinaphthyl two-armed ditosylate[5] (**4**) in 200 mL of purified dioxane was added (15 min) to a refluxing and stirred (under N_2) mixture of 8.0 g of 3-allylcatechol,[9] 6.9 g of 85% KOH, and 400 mL of butanol. The resulting mixture was refluxed for 7 h, cooled, and filtered. The filtrate was concentrated to give 37 g of oil which was chromatographed on 1 kg of neutral alumina. Elution of the column with 10 L of benzene–ether (7:3, v/v) gave on concentration and drying at 100 °C (50 μm) for 24 h 11.7 g (41%) of macrocycle. The 100-MHz ^1H NMR spectrum of this material in $CDCl_3$ gave a multiplet at δ 4.95 ($C{=}CH_2$) as well as a d of d at δ 1.81, whose integration indicated the presence of 71% of the allyl and 29% of the 1-propenyl derivative. Accordingly, the mixture was dissolved in 700 mL of dry benzene which was mixed at 25 °C with 10 mL of 1 M *t*-BuOK in *t*-BuOH for 6 h, conditions that completed the isomerization of the allyl to the propenyl derivative. The solution was extracted with three 200-mL portions of 0.5 M hydrochloric acid, dried, concentrated, and film dried at 100 °C (50 μm) for 24 h to give 11.1 g (95%) of cycle **20** as a colorless glass, M^+ 576. The ^1H NMR spectrum (100 MHz) in $CDCl_3$ gave δ 7.8 (m, naphthyl ArH, 4), 7.5–6.5 (complex m, naphthyl and benzo ArH and olefinic CH, 12), 6.2 (m, olefinic CH, 1), 4.0 (m, $ArOCH_2$, 7), 3.6 (m, CH_2OCH_2, 9), and 1.84 (d of d, J_1 = 7 Hz, J_2 = 2 Hz, CH_3, 3). Anal. Calcd for $C_{37}H_{36}O_6$: C, 77.06; H, 6.29. Found: C, 77.11; H, 6.25.

4-(3′-Hydroxypropyl)catechol. To a solution of 42.6 g of 4-allylveratrole[10] in 250 mL of dry THF was added 110 mL of a 0.1 M solution of diborane in THF, and the solution was stirred for 0.75 h. A solution of 1 mL of 3 M aqueous NaOH in 16 mL of water was added carefully, followed by 31 mL of 3 M aqueous NaOH, followed by careful addition of 42 mL of a 30% solution of hydrogen peroxide. The resulting mixture was stirred for 1 h and 120 g of K_2CO_3 and 100 mL of water were added, and the mixture was stirred for 1 h. The layers were separated and the THF layer was dried and concentrated to give 43.9 g of an oil. This material was distilled under vacuum to give three fractions: Fl, 0.64 g, bp 60–110 °C at (50 μm); F2, 34.5 g, bp 110–112 °C (50 μm); F3, 4.9 g, bp 112–113 °C (50 μm). Fraction F2 was shown by its ^1H NMR spectrum to be a 9:1 mixture of primary to secondary alcohol, and F3 contained <0.5% of secondary alcohol. Fractions F2 and F3 together provided 39.4 g (84%) of a 9.15:0.85 mixture of the primary to secondary alcohol. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.35; H, 8.12.

This veratrole derivative was demethylated as follows. A solution of 104 g of BBr_3 in 150 mL of dry CH_2Cl_2 was added to 35.0 g of the above mixture of alcohols dissolved in 400 mL of dry CH_2Cl_2 at −77 °C under N_2. The resulting solution was warmed to 25 °C over 1 h, poured into 1 kg of ice water, and stirred vigorously for 12 h. The layers were separated and the CH_2Cl_2 solution was dried and concentrated to give 3.5 g of olefinic material derived from the unwanted secondary alcohol. The aqueous layer was extracted with five 600-mL portions of ether and the combined extracts were dried, concentrated, and dried as a film at 110 °C (50 μm) for 15 h: wt 21.5 g (78%) of viscous oil. This 4-(3-hydroxypropyl)catechol was pure to TLC and gave: M^+ 168; ^1H NMR (CD_3COCD_3 containing several drops of D_2O) δ 6.7 (m, ArH, 3), 3.58 (t, *J* = 6.5 Hz, $CH_2OH(D)$, 2), 2.57 (m, $ArCH_2$, 2) and 1.83 (m, $CH_2CH_2CH_2$, 2). There was no trace of a d in the region of δ 1.2, attributable to a methyl group of a secondary alcohol. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.24.

2,3:4,5-Dinaphtho-13,14-[4-(4-oxabutyl)-1,2-benzo]1,6,9,12,-15,18-hexaoxacycloeicosa-2,4,13-triene (21). Application of procedure I to dinaphthyl two-armed ditosylate[5] (**4**) and 4-(3-hydroxypropyl)catechol gave cycle **21** in 46% yield as a colorless glass: ^1H NMR (100 MHz, $CDCl_3$) δ 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.7 (m, benzo ArH, 3), 4.0 (complex m, $ArOCH_2$, 8), 3.5 (complex m, CH_2OCH_2 and CH_2OH, 10), 2.57 (m, aryl-CH_2, 2), and 1.78 (m, $CH_2CH_2CH_2OH$, 3). Anal. Calcd for $C_{37}H_{38}O_7$: C, 74.73; H, 6.44. Found: C, 74.84; H, 6.56.

2,3:4,5-Dinaphtho-13,14-(3-aldehydo-1,2-benzo)-1,6,9,12,15,-18-hexaoxacycloeicosa-2,4,13-triene (22). Into 500 mL of CH_2Cl_2 at −77 °C was bubbled on ozone–oxygen mixture until the deep blue color did not intensify. This solution was added to a stirred solution of 5.8 g of cyclic alkene **21** in 125 mL of dry CH_2Cl_2 at −77 °C. The colorless solution was stirred for 0.3 h, 1.8 g of Zn was added, and the stirred solution was slowly warmed (5 h) to 25 °C. The solution was concentrated and the residue dissolved in dry THF, whereupon a solid separated. A portion of this material (aldehyde **22**) was purified as follows, and the remainder was used directly in the next reaction (**22** → **23**). The white solid (0.15 g) was recrystallized from THF to give cubic crystals of a 1:1 solvate (^1H NMR): mp 100–110 °C (bubbles, solidification, and remelting at 159–160 °C). The solid was heated at 100–110 °C at 50 μm for 24 h, and the amorphous aldehyde **22** was characterized: IR ($CDCl_3$) C=O band at 1695 cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) δ 10.36 (s, O=CH, 1), 7.8 (m, naphthyl ArH, 4), 7.5–6.9 (complex m, naphthyl and benzo ArH, 11), 4.1 and 3.6 (overlapping complex m, OCH_2, 16). Anal. Calcd for $C_{35}H_{32}O_7$: C, 74.45; H, 5.71. Found: C, 74.22; H, 5.80.

2,3:4,5-Dinaphtho-13,14-(3-hydroxymethyl-1,2-benzo)-1,6,9,-12,15,18-hexaoxacycloeicosa-2,4,13-triene (23). The remaining unpurified aldehyde **22** (see above) in 150 mL of THF was slowly added to 380 mg of $LiAlH_4$ in 150 mL of dry THF. The mixture was refluxed for 0.5 h, treated with 2.5 mL of water, filtered, and concentrated. The residue was chromatographed on 300 g of silica gel with $CHCl_3$–ethanol (49:1, v/v) as eluent. Alcohol **23** was eluted with 12 L of solvent, which when evaporated gave a glass. This material was film dried at 100 °C (50 μm) for 24 h to give 4.4 g (80% based on olefin **20**) of **23**: IR (KBr) OH band at 3440 cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) δ 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.8 (m, benzo ArH, 3), 4.72 and 4.34 (ABq, J_{AB} = 12 Hz, CH_2OH, 2) and 4.2–3.1 (complex m, CH_2O and OH, 7). Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05. Found: C, 74.03; H, 5.97. This material crystallized as a solvate from THF, mp 90–100 °C (bubbles).

2,3:4,5-Dinaphtho-13,14-(3-chloromethyl-1,2-benzo)-1,6,9,-12,15,18-hexaoxacycloeicosa-2,4,13-triene (24). A solution of 5.8 g of thionyl chloride in 210 mL of dry benzene was added dropwise to a solution of 12.8 g of alcohol **23** in 620 mL of dry benzene and 4 mL of dry pyridine. The mixture was refluxed for 1 h, filtered, and concentrated and the residue was dissolved in 500 mL of CH_2Cl_2. The solution was washed with water, dried, and concentrated to give 13.2 g (100% crude) of **24** as a yellow glass film dried at 70 °C (50 μm) for 1 h. A 100-mg sample was crystallized and recrystallized from THF to give a 1:1 solvate: mp 90–100 °C (bubbles). Anal. Calcd for $C_{35}H_{33}ClO_6 \cdot C_4H_8O$: C, 71.27; H, 6.29. Found: C, 71.27; H, 6.42. The sample when heated at 100 °C (50 μm) for 48 h gave **24** as a glass. Anal. Calcd for $C_{35}H_{33}ClO_6$: C, 71.86; H, 5.69. Found: C, 71.74; H, 5.69.

2,3:4,5-Dinaphtho-13,14-(3-azidomethyl-1,2-benzo)-1,6,9,12,-15,18-hexaoxacycloeicosa-2,4,13-triene (25). A mixture of 12.8 g of chloride **24**, 14 g of sodium azide, and 700 mL of 95% ethanol was stirred at reflux for 15 h and concentrated. The residue was partitioned between 500 mL of CH_2Cl_2 and 150 mL of water. The organic layer was washed with water, dried, and concentrated to give after film drying at 100 °C (50 μm) (2 h) 10.1 g (80%) of a glass. A 150-mg sample was chromatographed on neutral alumina wtih benzene–ether (4:1) as eluent to give azide **25** as a glass, whose IR spectrum ($CDCl_3$) showed a strong band at 2105 cm^{-1} (N_3 asymmetric stretch). Anal. Calcd for $C_{35}H_{33}N_3O_6$: C, 71.05; H, 5.58. Found: C, 71.00; H. 5.62.

2,3:4,5-Dinaphtho-13,14-(3-*N*-acetylaminomethyl-1,2-benzo)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (26). A solution of 9.8 g of crude azide **25** (see above) in 500 mL of dry THF was added slowly to 2.5 g of $LiAlH_4$ in 100 mL of dry THF. The resulting mixture was refluxed for 0.5 h, cooled, and treated carefully with 32 mL of water and 500 mL of CH_2Cl_2. The mixture was filtered, dried, and concentrated to give a glass. This amine (8.6 g) was dissolved in 240 mL of dry CH_2Cl_2 and 4.6 g of triethylamine, and the solution was treated with a solution of 1.61 g of acetyl chloride in 100 mL of dry CH_2Cl_2. The mixture was stirred for 0.5 h, washed with water, dried, and evaporated to give 8.2 g of glass. This material was chromatographed on 500 g of neutral alumina with ether–ethanol (99:1, v/v) as eluent. Fractions of 500 mL were collected. Fractions 12–24 were evaporated to give 5.6 g of a white solid which was crystallized from ether–benzene. This amide (**26**) as fine needles was dried at 165 °C at (50 μm) for 24 h to give 5.1 g (57%) of pure material: mp 193–194 °C; IR ($CDCl_3$) N–H band at 3333, C=O band at 1661 cm^{-1}; M^+ 607; ^1H NMR (100 MHz, $CDCl_3$) δ 7.8 (m, naphthyl, ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.8 (m, benzo ArH and NH, 4), 4.1 (complex m, $ArOCH_2$ and $ArCH_2N$, 10), 3.5 (complex m, CH_2OCH_2, 8), and 1.75 (s, CH_3, 3). Anal. Calcd for $C_{37}H_{37}NO_7$: C, 73.17; H, 6.14. Found: C, 73.27; H, 6.11.

2,3:4,5-Dinaphtho-13,14-[4-(3-chloropropyl)-1,2-benzo]-1,-6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (27). Alcohol **21** (4.0 g) in 70 mL of dry benzene and 2.5 mL of dry pyridine was treated with 1.6 g of thionyl chloride in 70 mL of dry benzene. The resulting mixture was refluxed for 3.5 h and stirred at 25 °C with 1 mL of water. The benzene layer was concentrated and the residue was chromatographed on 300 g of silica gel with $CHCl_3$ as eluting agent. Product was eluted with 3 L of $CHCl_3$, concentration of which gave after drying at 110 °C (50 μm) for 24 h 3.9 g (95%) of chloride **27**. Anal. Calcd for $C_{37}H_{37}ClO_6$:

C, 72.71; H, 6.10. Found: C, 72.70; H, 6.05.

2,3:4,5-Dinaphtho-13,14-[4-(3-carboxypropyl)-1,2-benzo]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (28). A solution of 8.0 g of ethyl bromide in 100 mL of dry THF was added slowly to 2.2 g of Mg turnings covered by 30 mL of dry THF under N_2. After about half the ethyl bromide had been added, a solution of 4.75 g of chloride **27** in 20 mL of dry THF was added to the remaining ethyl bromide solution, and the addition was completed. The resulting reaction mixture was refluxed for 8 h, cooled to −25 °C, and dry carbon dioxide gas was bubbled through the reaction mixture for 1 h. The solution was warmed to 25 °C and diluted with 10 mL of brine and the mixture was shaken. The organic layer was filtered and concentrated and the residue was dissolved in 200 mL of CH_2Cl_2. The solution was washed with dilute hydrochloric acid and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated and the residue was chromatographed on 300 g of silica gel with chloroform–ethanol–acetic acid (98:2:0.2, v/v/v) as eluting agent. Elution of the column with 1.5 L of solvent gave 0.5 g of byproducts. Elution with an additional 2 L of solvent gave product acid **28,** obtained as a glass by evaporation of the solvent and film drying at 120 °C (50 μm) for 24 h; wt 3.6 g (74%); IR ($CDCl_3$) broad OH band at 3000, C=O band at 1720 cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) δ 9.3 (br s, CO_2H, 1), 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.68 (narrow m, benzo ArH, 3), 4.0 and 3.5 (overlapping complex m, CH_2O, 16), 2.56 and 2.31 (overlapping m's; former is phenyl-CH_2–, latter is HO_2CCH_2–, 4) and 1.92 (m, $CH_2CH_2CH_2$, 2); mass spectrum base peak M^+ 622. Anal. Calcd for $C_{38}H_{38}O_8$: C, 73.29; H, 6.15. Found: C, 72.99; H, 6.34.

2,3:4,5-Bis[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (29). Procedure 2. A solution of 12.6 g of tetrol **8**[6] in 900 mL of THF was stirred at 25 °C under N_2 for 30 min. To the clear solution was added 4.5 g of KOH dissolved in 80 mL of water. The mixture was warmed to 65 °C (homogeneous) and with stirring 26 g of pentaethylene glycol ditosylate[4,11] dissolved in 100 mL of THF was added. The solution was refluxed for 48 h, cooled, concentrated to 200 mL at 30 mm, and partitioned between water and CH_2Cl_2. The water layer was extracted with additional CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to 100 mL. This solution was chromatographed on 500 g of neutral alumina packed in CH_2Cl_2. Elution of the column with 2 L of CH_2Cl_2, 2 L of 1% 2-propanol–CH_2Cl_2, and 2 L of 2% 2-propanol–CH_2Cl_2 produced after removal of solvents 12.0 g (60%) of **29** as a colorless glass, which tenaciously retains solvent. When heated as a thin film at 145 °C (0.05 mm) for 6 h, the solvent evaporated. A crystalline sample of **29,** mp 132–134 °C, was obtained by concentrating a 2-propanol solution (1 g in 50 mL) at 25 °C. The solid material after drying at 25 °C for 48 h and 0.1 mm still contained a trace (^1H NMR) of 2-propanol. **29:** ^1H NMR (100 MHz, $CDCl_3$) δ 7.90 (s, ArH^4, 2), 7.85 (m, ArH^5, 2), 7.28 (m, ArH, 6), 4.95 (AB q, J_{AB} = 13 Hz, $ArCH_2O$, 4), and 7.28 (complex m, OCH_2, 20); mass spectrum base peak M^+ 548 (see Table V for analysis).

(−)-(*S*)-2,3:4,5-Bis(1,2-[3-(2,5-dioxa-4-oxohexyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [(−)-(*S*)-38]. Procedure 3. To a solution of optically pure (−)-(*S*)-**29** (Table V) (5.8 g) in 250 mL of THF was added NaH as a 50% suspension in oil (2.4 g, 50 mmol) and the mixture was stirred at 25 °C for 2 h. Methyl bromoacetate (7.6 g) was added to the above suspension and the mixture was heated to reflux for 6.5 h. The reaction mixture was cooled and filtered and the solid was washed with THF. The combined filtrate was evaporated to an oil that was chromatographed on 150 g of silica gel. Elution of the column with 1.4 L of CH_2Cl_2 gave nonnaphthalene-containing products (^1H NMR). Elution with 3.5 L of 2% methanol–ether (by volume) gave (−)-(*S*)-**38.** The eluate was evaporated to give 3.2 g (44%) of this product as a glass, which was dried at 165 °C (0.07 mm) for 1 h: $[\alpha]^{25}_{546}$ −25.7° (*c* 1.0, THF); M^+ 692; 100 MHz ^1H NMR ($CDCl_3$) δ 7.7–8.05 (m, ArH, 4), 7.0–7.5 (m, ArH, 6), 5.0 (s, $ArCH_2O$, 4), 4.35 (s, OCH_2CO_2, 4), 3.80 (s, OCH_3, 6), 2.8–3.8 (m, OCH_2CH_2O, 20). Table V records the analysis.

2,3-(1,2-[3-(2,5-Dioxa-4-oxohexyl)naphtho])-4,5-[1,2-(3-methylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (Methyl Ester of 49). Application of procedure 3 to monomethylmonool **34** (Table V) gave the methyl ester of **49** as a glass (72%); M^+ 604; ^1H NMR (60 MHz, $CDCl_3$) δ 8.10–6.84 (m, ArH, 10), 4.98 (s, $ArCH_2$, 2), 4.32 (s, CH_2CO_2, 2), 4.05–2.76 (m, CH_2O, 20), 3.72 (s, OCH_3, 3) and 2.55 (s, $ArCH_3$, 3). Anal. Calcd for $C_{35}H_{40}O_9$: C, 69.52; H, 6.67. Found; C, 69.29; H, 6.48.

2,3-(1,2-[3-(2,5-dioxa-4-oxohexyl)naphtho])-4,5-[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxyacycloeicosa-2,4-diene (Methyl Ester of 51). Application of a modified procedure 3 to diol **29** (Table V) gave the methyl ester of monoacid **51.** To a solution of 5.5 g of **29** in 500 mL of THF under N_2 was added 3.0 g of NaH (50% mineral oil dispersion). The mixture was heated to reflux and 2.2 g of methyl bromoacetate in 25 mL of THF was added, and the mixture was refluxed for 12 h, cooled, filtered, and evaporated under vacuum. The residue was shaken with 400 mL each of water and CH_2Cl_2 and the organic layer was dried and concentrated. The residue was chromatographed on 200 g of silica gel and the column was washed with 2 L of CH_2Cl_2, 2 L of CH_2Cl_2–methanol (99:1, v/v), and 2 L of CH_2Cl_2–methanol (49:1, v/v). Then 2 L of 19:1 (v/v) CH_2Cl_2–methanol gave 2.2 g (35%) of diester **38,** identified by TLC and ^1H NMR spectrum. Elution of the column with 2 L of 9:1 and 3 L of 4:1 (v/v) CH_2Cl_2–methanol gave upon evaporation and drying 0.60 g (10%) of the methyl ester of monoacid **51** as a glass: M^+ 620; ^1H NMR (60 MHz, $CDCl_3$) δ 8.02 (s, ArH^4, 1), 7.86 (s, ArH at ArH^4, 1), 7.95–6.85 (m, ArH, 8), 4.88 (s, $ArCH_2O$, 2), 4.90 (ABq, CH_2OH, 2), 4.26 (s, OCH_2CO_2, 2), 3.75 (s, OCH_3, 3), and 3.92–2.80 (m, OCH_2, 20). Anal. Calcd for $C_{35}H_{40}O_{10}$: C, 67.73; H, 6.50. Found: C, 67.90; H, 6.51.

Application of this same procedure to optically pure (+)-(*R*)-**29** gave (14%) the methyl ester of the monoacid, (−)-(*R*)-**51,** identified by TLC and ^1H NMR spectral comparisons with racemic ester.

(−)-(*S*)-2,3:4,5-Bis(1,2-[3-(2,5-dioxa-4-oxopentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [(−)-(*S*)-44]. Procedure 4. A mixture of (−)-(*S*)-**38** (Table V) (5.2 g) and barium hydroxide octahydrate (7.1 g) in 250 mL of methanol was heated at reflux for 4 h and evaporated to dryness. The residue was dissolved in water and the aqueous solution was washed with a mixture of CH_2Cl_2 and ether. The aqueous layer was filtered and acidified with hydrochloric acid to pH 1 to give a milk-like emulsion, which was extracted twice with CH_2Cl_2. The combined extracts were washed once with 5% aqueous hydrochloric acid and three times with water and dried. Evaporation of the CH_2Cl_2 gave 4.65 g (90%) of optically pure (−)-(*S*)-**44** as a glass. A sample dried as a thin film at 165 °C (0.07 mm) for 1 h gave: $[\alpha]^{25}_{546}$ +76.2° (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_{546}$ −24.4° (*c* 1.0, THF); M^+ 664; 100-MHz ^1H NMR ($CDCl_3$) δ 7.7–8.1 (m, ArH, 4), 6.9–7.5 (m, ArH, 6), 4.97 (s, $ArCH_2O$, 4), 4.30 (s, OCH_2CO_2, 4), 3.0–4.0 (m, OCH_2CH_2O, 20). The analysis is given in Table V.

Procedure 4 when applied to the hydrolysis of the methyl ester of **49** gave (85%) **49** as a glass: M^+ 590; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.15–6.95 (m, ArH, 10), 5.10 (s, $ArCH_2$, 2), 4.42 (s, CH_2CO_2, 2), 4.20–2.95 (m, OCH_2, 20), and 2.60 (s, $ArCH_3$, 3). Table V records the analysis.

Procedure 4 when applied to the methyl ester of monoacid **51** gave (77%) acid **51** as a glass: M^+ 606; ^1H NMR (60 MHz, $CDCl_3$) δ 8.07 (s, ArH^4, 1), 7.96 (s, ArH^4, 1), 7.95–6.88 (m, ArH, 8), 4.90 (m, $ArCH_2OH$ and $ArCH_2OCH_2$, 4), 4.25 (s, OCH_2CO_2, 2), and 3.92–2.80 (m, OCH_2, 20). Table V records its analysis.

Procedure 4 applied to the methyl ester of monoacid (+)-(*R*)-**51** gave (82%) (+)-(*R*)-**51** as a glass: $[\alpha]^{25}_{578}$ −68.3°, $[\alpha]^{25}_{546}$ −80.4° (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_{578}$ +20.7°, and $[\alpha]^{25}_{546}$ +24.2° (*c* 1.0, THF). Table V records the analysis.

2,3:4,5-Bis[1,2-(3-chloromethylnaphto)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (52) and (−)-(*S*)-52. Procedure 5. To a suspension of 4.0 g of **29** in 50 mL of benzene was added 4.0 g of thionyl chloride at 25 °C. The mixture became homogeneous, and after stirring at 25 °C for 8 h the solvent was evaporated under vacuum and the residue was dissolved in 100 mL of CH_2Cl_2. The solution was extracted with a 100-mL portion of sodium bicarbonate saturated water, and the water layer was washed with 50 mL of CH_2Cl_2. The combined organic extracts were dried, evaporated, and chromatographed on 100 g of silica gel. The column was washed with 500 mL of CH_2Cl_2 and 500 mL of CH_2Cl_2–ether (19:1, v/v). Product **52** was eluted with 2 L of CH_2Cl_2–ether (9:1) and 1 L of 4:1 (v/v) CH_2Cl_2–ether as an oil: wt 3.9 g (91%); M^+ 584; ^1H NMR (60 MHz, $CDCl_3$) δ 8.05 (s, ArH^4, 2), 7.98–7.14 (m, ArH, 8), 5.50 (ABq, CH_2Cl, 4), and 3.93–2.75 (m, OCH_2, 20). Table V reports the analysis. Optically pure enantiomer, (−)-(*S*)-52, similarly prepared from optically pure (−)-(*S*)-**29,** gave $[\alpha]^{25}_{578}$ −7.0°, $[\alpha]^{25}_{546}$ −9.5°, $[\alpha]^{25}_{436}$ −38.4° (*c* 1.0, $CHCl_3$).

2,3:4,5-Bis(1,2-[3-(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,-6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (53) and (+)-(*S*)-53. Procedure 6. To a stirred solution of racemic **52** (2.0 g) and 3.7 g of thioglycolic acid in 200 mL of THF under N_2 was added 3.2 g of NaOH dissolved in 30 mL of water. The mixture was refluxed for 20 h, cooled, and concentrated under vacuum to 20 mL. The solution was diluted to 100 mL with water and 6 N hydrochloric acid was added until a pH of 1 was obtained. An oil separated and the mixture was allowed to stand at 25 °C for 10 h. The aqueous solution was decanted and the oily residue was washed three times with 50 mL of water. The residue was dissolved in 150 mL of CH_2Cl_2 and the solution was washed with water, dried, and evaporated under vacuum. The residue was dried

Table V. Compound Numbers, Procedures, Yields, Physical Properties, and Analyses of Macrocycles

Compd no.			Product							
						Anal.				
						Calcd for, %			Found, %	
Starting material[a]	Product	Procedure no.[b]	Mp, °C	Yield, %	$[\alpha]^{25}_{546}$ (c 1.0, THF)[c]	Formula	C	H	C	H
(−)-(*S*)-8	(−)-(*S*)-29	2	Glass	55	−34.0°	$C_{32}H_{36}O_8$	70.05	6.61	69.89	6.82
8	29	2	132–134	60		$C_{32}H_{36}O_8$	70.05	6.61	69.91	6.70
(−)-(*S*)-8	(−)-(*S*)-30	2	Glass	6	−56.1°	$C_{30}H_{32}O_7$	71.41	6.39	71.45	6.45
8	30	2	Glass	10		$C_{30}H_{32}O_7$	71.41	6.39	71.21	6.53
(+)-(*R*)-8	(−)-(*R*)-31	2	Glass	57	−16.4°	$C_{34}H_{40}O_9$	68.90	6.80	69.02	6.80
8	31	2	Glass	50		$C_{34}H_{40}O_9$	68.90	6.80	68.73	6.98
9	32	2	136–137	50		$C_{31}H_{34}O_7$	71.80	6.61	71.57	6.64
9	33	2	151–152	31		$C_{29}H_{30}O_6$	73.39	6.37	73.33	6.26
10	34	2	159	59		$C_{32}H_{36}O_7$	72.16	6.81	72.12	7.06
11	35	2	Glass	55		$C_{36}H_{43}NO_8$	70.00	7.02	69.76	7.22
12	36	2	Glass	65		$C_{40}H_{50}N_2O_8$	69.95	7.34	69.71	7.38
13	37	2	Glass	64		$C_{36}H_{46}N_2O_6$	71.73	7.69	71.70	7.62
(−)-(*S*)-24	(−)-(*S*)-38	3	Glass	44	−25.7°	$C_{38}H_{44}O_{12}$	65.87	6.40	65.99	6.27
24	38	3	Glass	60		$C_{38}H_{44}O_{12}$	65.87	6.40	65.63	6.27
(−)-(*S*)-25	(−)-(*S*)-39	3	Glass	51	−95.7°	$C_{36}H_{40}O_{11}$	66.65	6.22	66.50	6.05
25	39	3	Glass	55		$C_{36}H_{40}O_{11}$	66.65	6.22	66.46	6.15
(−)-(*R*)-26	(−)-(*R*)-40	3	Glass	54	−19.5°	$C_{40}H_{48}O_{13}$	65.20	6.57	65.05	6.50
26	40	3	Glass	50		$C_{40}H_{48}O_{13}$	65.20	6.57	65.06	6.39
28	41	3	Glass	70		$C_{34}H_{38}O_9$	69.14	6.48	68.95	6.71
29	42	3	128–130	71		$C_{32}H_{34}O_8$	69.91	6.05	70.09	6.26
35	43	3	Glass	35		$C_{39}H_{47}NO_{10}$	67.91	6.87	67.98	6.89
(−)-(*S*)-38	(−)-(*S*)-44	4	Glass	90	−24.4°	$C_{36}H_{40}O_{12}$	65.05	6.07	65.00	6.23
38	44	4	Glass	80		$C_{36}H_{40}O_{12}$	65.05	6.07	64.87	6.28
(−)-(*S*)-39	(−)-(*S*)-45	4	Glass	65	−107.4°	$C_{34}H_{36}O_{11}$	65.79	5.85	65.86	5.94
39	45	4	Glass	85		$C_{34}H_{36}O_{11}$	65.79	5.85	65.92	5.87
(−)-(*R*)-40	(−)-(*R*)-46	4	Glass	50	−15.0°	$C_{38}H_{44}O_{13}$	64.39	6.26	64.18	6.06
40	46	4	Glass	75		$C_{38}H_{44}O_{13}$	64.39	6.26	64.14	6.42
41	47	4	Glass	70		$C_{33}H_{36}O_9$	68.74	6.29	68.95	6.63
42	48	4	128–130	35		$C_{31}H_{32}O_8$	69.91	6.05	70.09	6.26
31	49	3,4	Glass	85		$C_{34}H_{38}O_9$	69.14	6.48	69.78	6.47
43	50	4[e]	Glass	65		$C_{38}H_{45}NO_{10}$	67.53	6.71	67.41	6.74
24	51	3,4	Glass	77		$C_{34}H_{38}O_{10}$	67.31	6.31	67.63	6.29
(+)-(*R*)-24	(+)-(*R*)-51	3,4	Glass	82	+24.2°	$C_{34}H_{38}O_{10}$	67.31	6.31	67.30	6.21
24	52	5	Glass	91		$C_{32}H_{34}Cl_2O_6$	65.61	5.86	65.89	5.91
(−)-(*S*)-24	(−)-(*S*)-52	5	Glass	81	−9.5°[d]	$C_{32}H_{34}Cl_2O_6$	65.61	5.86	65.87	6.01
52	53	6	Glass	96		$C_{36}H_{40}O_{10}S_2$	62.06	5.79	61.90	6.16
(−)-(*S*)-52	(+)-(*S*)-53	6	Glass	72	+12.0°	$C_{36}H_{40}O_{10}S_2$	62.06	5.79	62.21	6.01
52	54	6	Glass	97		$C_{38}H_{44}O_{10}S_2$	62.98	6.12	62.86	6.15
(−)-(*S*)-52	(−)-(*S*)-54	6	Glass	58	−33.6°	$C_{38}H_{44}O_{10}S_2$	62.98	6.12	62.67	6.27
52	55	7	140	91		$C_{38}H_{40}O_{14}$	63.33	5.59	63.15	5.82
55	56	7	Glass	92		$C_{36}H_{40}O_{10}$	68.34	6.37	68.30	6.51
(−)-(*S*)-52	(−)-(*S*)-56	7	Glass	85	−94°[d]	$C_{36}H_{40}O_{10}$	68.34	6.37	68.10	6.40

[a] Optically pure when optically active, ref 6. [b] See Experimental Section. [c] Unless otherwise noted. [d] *c* 1. $CHCl_3$. [e] Lithium hydroxide was substituted for barium hydroxide.

at 95 °C (5 μm) for 1 h to give 2.3 g (96%) of **53** as a glass: M^+ 696; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 8.00–6.90 (m, ArH, 8), 4.22 (ABq, $ArCH_2S$, 4), 3.40 (s, SCH_2CO_2, 4), and 4.10–2.90 (m, OCH_2, 20). Table V records the analysis.

Optically pure (+)-(*S*)-**53** was similarly prepared: $[\alpha]^{25}_{546}$ +204° (*c* 1.3, $CHCl_3$) and $[\alpha]^{25}_{546}$ +12.0° (*c* 1.0, THF). Table V records the analysis.

2,3:4,5-Bis(1,2-[3-(6-oxa-5-oxo-2-sulfahexyl)naphtho])-1,-6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (54) and (−)-(*S*)-54 by Procedure 6. Racemic **54** was similarly prepared from racemic **52** except β-sulfhydrylpropionic acid was substituted for thioglycolic acid. The product gave: M^+ 724; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 8.02–6.90 (m, ArH, 8), 4.18 (AB q, $ArCH_2$, 4), and 4.20–2.50 (m, OCH_2, $SCH_2CH_2CO_2$, 28). Table V records the analysis.

Optically pure (−)-(*S*)-**54** prepared from optically pure (−)-(*S*)-**52** gave $[\alpha]^{25}_{546}$ +61.5° (*c* 1.15, $CHCl_3$) and $[\alpha]^{25}_{546}$ −33.6° (*c* 1.21, THF). Table V records the analysis.

2,3:4,5-Bis(1,2-[3-(2-carboxy-4-oxa-3-oxobutyl)naph-tho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (55), 2,3:4,5-Bis(1,2-[3-(4-oxa-3-oxobutyl)naphtho])-1,6,9,12,15,18-hex-aoxacycloeicosa-2,4-diene (56), and (−)-(*S*)-56. Procedure 7. To a solution under N_2 of 3.0 g of **52** and 2.0 g of dimethyl malonate in 100 mL of dry toluene was added with stirring 0.720 g of NaH (50% mineral oil dispersion). The mixture was stirred for 1 h at 25 °C, at reflux for 2 h, and an additional 6 h at 25 °C. The solution was cooled and shaken with 200 mL of CH_2Cl_2 and 200 mL of water. The aqueous layer was extracted with 50 mL of CH_2Cl_2 and the combined organic layers were dried and evaporated under vacuum. The residue was chromatographed on 100 g of silica gel. The column was washed with 1 L of CH_2Cl_2, 1 L of 49:1 (v/v) CH_2Cl_2–ether, and 1 L of 19:1 (v/v) CH_2Cl_2–ether. Elution of the product (tetraester) came with 2 L of 9:1 and 2 L of 4:1 (v/v) CH_2Cl_2–ether: wt 2.6 g (65%) of glass; M^+ 776; ^1H NMR (60 MHz, $CDCl_3$) δ 7.92–6.90 (m, ArH, 10), 4.10 (m, $CH(CO_2CH_3)_2$, 2) and 3.90–2.70 (m, $ArCH_2$, OCH_2, OCH_3, 36). Anal. Calcd for $C_{42}H_{48}O_{14}$: C, 64.94; H, 6.23. Found: C, 64.85; H, 6.16.

To a solution of 2.0 g of the above tetraester in 100 mL of ethanol was added 2.0 g of NaOH in 15 mL of water. The mixture was refluxed for 8 h, concentrated under vacuum to 10 mL and diluted with 75 mL of water. The solution was acidified with 6 N hydrochloric acid to a pH of 1. Tetraacid **55** crystallized and was collected, washed with water, and vacuum dried at 25 °C to give 1.7 g (91%) of white solid, mp 140 °C, with loss of carbon dioxide: ^1H NMR (60 MHz, Me_2SO-d_6) δ 8.04–6.80 (m, ArH, 10) and 4.20–3.16 (m, CH_2O, $CH_2CH(CO_2H)_2$, 26). Table V records the analysis.

Tetraacid **55**, 0.36 g, was heated at 160 °C (30 mm) for 2 h. The resulting oil was cooled and dissolved in 50 mL of CH_2Cl_2 and the solution was washed with water and dried. The solution was evaporated under vacuum and dried to give 0.30 g (92%) of **56** as a glass; M^+ 632; ^1H NMR (100 MHz, CD_3CO_2D) δ 8.0–6.8 (m, ArH, 10) and 4.5–2.60

(m, CH_2O, $ArCH_2CH_2CO$, 28). Table V records the analysis.

By procedure 7 optically pure (−)-(*S*)-**52** was converted to optically pure (−)-(*S*)-**56.** The tetraester intermediate was obtained in 44% yield (glass): $[\alpha]^{25}_{578}$ −64.7°, $[\alpha]^{25}_{546}$ −75.5°, $[\alpha]^{25}_{436}$ −152.4° (c 1.0, $CHCl_3$). This material was decarboxylated to give (−)-(*S*)-**56** by the above method. Table V records the analyses.

2,3:4,5-Bis[1,2-(6-bromonaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (58). To 3 g of parent cycle **57**[4] dissolved in 100 mL of CH_2Cl_2 was added 0.3 mL of bromine and the reaction mixture was heated to reflux. After 1 h, 0.35 mL more bromine was added and the solution was refluxed an additional 7.5 h. The solution was cooled and shaken with 25 mL of a 10% $NaHSO_3$ solution. The organic phase was separated, washed successively with water, saturated $NaHCO_3$ solution, and brine, and dried. Evaporation of the solvent left 4.17 g of an orange oil. This material was dissolved in ether and the solution was cooled to give 2.65 g (67%) of **58:** mp 138–139.5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 3.40–3.62 (m, CH_2OCH_2, 16), 3.86–4.26 (m, $ArOCH_2$, 4), 7.40 (ArH^3), 7.76 (ArH^4, $J_{3,4}$ = 9 Hz), 7.93 (ArH^5), 7.20 (ArH^7, $J_{5,7}$ = 2 Hz), 6.90 (ArH^8, $J_{7,8}$ = 9 Hz). This ^1H NMR spectrum is uniquely consistent with the bromines being substituted in the 6- and 6′-positions of **58.** Anal. Calcd for $C_{30}H_{30}O_6Br_2$: C, 55.74; H, 4.68. Found: C, 55.98; H, 4.55.

2,3:4,5-Bis[1,2-(6-acetylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (59). Aluminum chloride (4.55 g) was added to 21.6 mL of nitrobenzene and the mixture was cooled to 0 °C. Acetyl chloride (2.52 g) and parent cycle **57**[4] (2.01 g) were then added in rapid succession and the mixture was stirred at 0 °C for 1 h. The cold mixture was stirred into an ice-concentrated hydrochloric acid mixture, which was subsequently extracted with CH_2Cl_2. The organic phase was washed successively with water, saturated $NaHCO_3$ solution, and brine and dried. Solvent was evaporated under reduced pressure to give an oil that was chromatographed on 100 g of neutral alumina. Fractions (100 mL) were collected of eluent. After 500 mL of ether eluate, 1% ethanol (by volume) in ether brought off the desired product in fractions 13–17, which on evaporation gave 0.982 g of **59:** mp 107–109 °C. Recrystallization of this material from acetone–hexane gave: 0.86 g (36%); mp 103–104 °C; IR (KBr) strong band at 1675 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 2.5 (s, CH_3, 6), 3.30–3.58 (m, CH_2OCH_2, 16), 3.92–4.34 (m, $ArOCH_2$, 4), 7.50 (ArH^3), 8.04 (ArH^4, $J_{3,4}$ = 9 Hz), 8.46 (ArH^5), 7.72 (ArH^7, $J_{5,7}$ = 2 Hz), 7.10 (ArH^8, $J_{7,8}$ = 9 Hz). Anal. Calcd for $C_{34}H_{36}O_8$: C, 55.74; H, 4.68. Found: C, 55.98; H, 4.55.

2,3:4,5-Bis[1,2-(6-chloromethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (60). Procedure 8. To 2.0 g of parent cycle **57**[4] and 10 g of chloromethyl methyl ether in 25 mL of $CHCl_3$ stirred at −60 °C was added (15 min) 3 mL of anhydrous stannic chloride. The solution was stirred for 1 h at −60 °C and shaken with 50 mL of water and 100 mL of CH_2Cl_2. The organic layer was washed with 100 mL of saturated $NaHCO_3$ solution, dried, and concentrated. The residue was chromatographed on 75 g of silica gel and the column was washed with 500 mL of CH_2Cl_2 and 500 mL of 19:1 (v/v) CH_2Cl_2–ether. Product was eluted with 1 L of 4:1 and 2 L of 1:1 (v/v) CH_2Cl_2–ether to give 1.2 g (50%) of **60** as a glass: M^+ 584; ^1H NMR (60 MHz, $CDCl_3$) δ 7.90–7.02 (m, ArH, 10), 4.62 (s, $ArCH_2$, 4), 4.02 (m, $ArOCH_2$, 4), and 3.70–3.18 (m, OCH_2, 16). Anal. Calcd for $C_{32}H_{34}Cl_2O_6$: C, 65.61; H, 5.86. Found: C, 65.58; H, 5.80.

2,3:4,5-Bis(1,2-[3,6-di(chloromethyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (61). Procedure 8 applied to di(chloromethyl) cycle **52** gave **61** (82%) as a glass: M^+ 680; ^1H NMR (60 MHz, $CDCl_3$) δ 8.00 (s, ArH^4, 2), 7.80 (s br, ArH^5, 2), 7.34–6.90 (m, $ArH^{7,8}$, 4), 4.98 (ABq. 3,3′-CH_2Cl, 4), 4.64 (s, 6,6′-CH_2Cl, 4), and 4.05–2.90 (m, OCH_2, 20). Anal. Calcd for $C_{34}H_{36}Cl_4O_6$: C, 59.83; H, 5.33. Found: C, 61.01; H, 5.67.

2,3:4,5-Bis[1,2-(6-carboxynaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (62). To a solution of 32 g of KOH in 100 mL of water at 5 °C was added 24 g of bromine. A solution of 4.5 g of diacetyl compound **59** in 200 mL of THF was added and the resulting mixture was held at reflux for 12 h with vigorous stirring. The reaction mixture was cooled, 100 mL of 10% $NaHSO_3$ solution was added, and the solution was concentrated under vacuum to 150 mL. The aqueous solution was diluted with 300 mL of water, washed with 200 mL of ether, and acidified with 6 N HCl to pH 1. The product that separated was collected, washed with water, and dried at 100 °C (50 μm) to give 3.8 g (84%) of diacid **62,** which gave: mp 291–292 °C (from methanol); ^1H NMR (100 MHz, $(CD_3)_2SO$) δ 7.70 (m, ArH^3 and ArH^7, 4), 8.24 (d, ArH^4, $J_{3,4}$ = 9 Hz, 2), 8.61 (d, ArH^5, $J_{5,7}$ = 2 Hz, 2), 6.98 (d, ArH^8, $J_{7,8}$ = 9 Hz, 2), 4.16 (m, $ArOCH_2$, 4), and 3.36 (m, CH_2O, 16). Anal. Calcd for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59. Found: C, 66.53; H, 5.63.

2,3:4,5-Bis[1,2-(6-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (63). Procedure 9. To a refluxing solution of 3.8 g of $LiAlH_4$ in 300 mL of THF was added, via Soxhlet extraction, 4.0 g of diacid **62.** The mixture was refluxed for 16 h and cooled and ethanol was cautiously added. The mixture was shaken with 500 mL of ether and 200 mL of 6 N hydrochloric acid and the resulting mixture was stirred for 8 h. The ether layer was separated and the aqueous layer extracted with two 200-mL portions of ether. The combined organic layers were washed with 100 mL of saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on 150 g of alumina. The column was washed with 2 L of ether and the product eluted with ether–2-propanol, 2 L of 49:1 and 2 L of 19:1 (v/v), to give 2.8 g (74%) of diol **63** as a glass: M^+ 548; ^1H NMR (60 MHz, $CDCl_3$) δ 7.88–7.00 (m, ArH, 10), 4.62 (s, $ArCH_2$, 4), and 4.22–3.05 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{32}H_{36}O_8$: C, 70.06; H, 6.61. Found: C, 70.22; H, 6.59.

2,3:4,5-Bis(1,2-[6-(2,5-dioxa-4-oxopentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (65). By procedure 3, diol **63** was converted with methyl bromoacetate to the dimethyl diester **65** (55%), which was a glass; M^+ 692; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98–7.04 (m, ArH, 10), 4.72 (s, $ArCH_2$, 4), 4.16 (s, CH_2CO_2, 4), 3.73 (s, OCH_3, 6), and 4.24–3.10 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{38}H_{44}O_{12}$: C, 65.88; H, 6.40. Found: C, 65.85; H, 6.60.

By procedure 4, this diester was hydrolyzed to diacid **65** as a glass (75%): M^+ 664; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98–7.00 (m, ArH, 10), 4.70 (s, $ArCH_2$, 4), 4.10 (s, CH_2CO_2, 4), and 4.20–3.20 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{36}H_{40}O_{12}$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.11.

2,3:4,5-Bis(1,2-[6-(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (66). By procedure 6 the bis(chloromethyl) cycle **60** was converted to diacid **66,** which was an oil (75%): M^+ 696; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.00–6.85 (m, ArH, 10), 3.96 (s, $ArCH_2$, 4), 4.15 (m, $ArOCH_2$, 4), 3.50 (m, OCH_2, 16), and 3.18 (s, CH_2CO_2, 4). Anal. Calcd for $C_{36}H_{40}O_{10}S_2$: C, 62.06; H, 5.79. Found: C, 61.94; H, 5.71.

2,3:4,5-Bis(1,2-[3,6-di(hydroxymethyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (64). Tetrachloro compound **61** was subjected to acetolysis to produce the tetraacetate of **64** as follows. To an acetic acid solution (150 mL), 1 M in KOAc, was added 5.50 g of **61** and the solution was refluxed for 18 h. The solution was cooled and shaken with a mixture of 400 mL each of water and CH_2Cl_2 and the organic layer was washed with two 100-mL portions of $NaHCO_3$-saturated water, dried, and evaporated. The product was chromatographed on 100 g of silica gel and the column was washed with 250 mL of CH_2Cl_2 and 0.5 L of 19:1 and 0.5 L of 9:1 (v/v) CH_2Cl_2–ether. The tetraacetate was eluted with CH_2Cl_2–ether, 1 L of 4:1 and 2 L of 1:1 (by volume), to give 4.8 g (76%) of the tetraacetate of **64** as a glass: M^+ 776; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98 (s, ArH^4, 2), 7.83 (s br, ArH^5, 2), 7.10 (m, $ArH^{7,8}$, 4), 5.50 (s. 3,3′-$ArCH_2$, 4), 5.20 (s, 6,6′-$ArCH_2$, 4), 3.82–2.80 (m, OCH_2CH_2O, 20), 2.18 (s, 3,3′-$COCH_3$, 6), and 2.05 (s, 6,6′-$COCH_3$, 6). Anal. Calcd for $C_{42}H_{48}O_{14}$: C, 64.94; H, 6.23. Found: C, 64.90; H. 6.15.

To a refluxing solution of 3.8 g of $LiAlH_4$ in 300 mL of THF under N_2 was added dropwise a solution of 4.8 g of the above tetraacetate in 150 mL of THF. The mixture was refluxed for 8 h and cooled to 5 °C, ethanol was cautiously added, and the mixture was shaken with 200 mL of 6 N hydrochloric acid and 300 mL of ether. The aqueous layer was washed with three 150-mL portions of 2:1 ether–THF and combined with the original organic layer. The solution was dried and evaporated under reduced pressure to give 3.4 g (90%) of tetrol **64** as a glass; M^+ 608; ^1H NMR (60 MHz, $CDCl_3$) δ 7.82 (s, ArH^4, 2), 7.72 (s, br, ArH^5, 2), 7.00 (m, $ArH^{7,8}$,4), 4.82 (ABq, 3,3′-$ArCH_2$, 4), 4.63 (s, 6,6′-$ArCH_2$, 4) and 4.20–2.70 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{34}H_{40}O_{10}$: C, 67.09; H, 6.62. Found: C, 66.82; H, 6.90.

2,3:4,5-Bis(1,2-[3,6-di(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (67). By procedure 6 except that the relative amount of thioglycolic acid was doubled, tetrachloride **61** was converted to tetraacid **67** (96%) as a glass (no M^+ observed): ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 7.86 (s, ArH^5, 2), 7.40–6.90 (m, $ArH^{7,8}$, 4), 4.20 (s, 3,3′-$ArCH_2$, 4), 3.95 (s, 6,6′-$ArCH_2$, 4), 3.40 (s, 3,3′-CH_2CO_2, 4), 3.18 (s, 6,6′-CH_2CO_2, 4), and 4.30–2.62 (m, OCH_2, 20). Anal. Calcd for $C_{42}H_{48}O_{14}S_4$: C, 55.73; H, 5.35. Found: C, 56.04; H, 5.43.

Solubilization in Deuteriochloroform of Crystalline Amine Salts by Complexation with Various Host Compounds. Tetraphenylborate salts of t-$BuNH_3^+$, $C_6H_5CH(CH_3)NH_3^+$, and $C_6H_5CH(CO_2CH_3)NH_3^+$ ions were prepared[18] by adding an aqueous solution of the hydrochloride of the amine to an aqueous solution of sodium tetraphenylborate. The precipitated salt was filtered, water washed, and dried at 50 °C (50 μm). The other salts were made by standard procedures or purchased. The abilities of various hosts to solubilize these amine salts were determined as follows. The cyclic

ether (~90 mg) was dissolved in 0.4 mL of $CDCl_3$ and its 100-MHz ^1H NMR spectrum recorded. Excess salt (3–4 mol per mole of cyclic ether) was shaken with this solution, which was then filtered, and the ^1H NMR spectrum again taken. The relative number of moles of the cyclic ether to the dissolved salt was determined (±5%) by integrating the appropriate signals of the protons of the cycle vs. those of the salt. After the spectra were run, all solutions were returned to contact with the excess salt, and the mixtures were shaken intermittently for 24 h without spectral change. With each salt, a parallel experiment was performed in which the host was absent. Unless noted otherwise, no signal was observed for the salt in the absence of the host, indicating the salt alone to be too insoluble to be detected. Table I records the results.

Extraction into Deuteriochloroform from Deuterated Water of Amine Salts by Complexation with Various Host Compounds. Hosts (~90 mg) were dissolved in 0.7 mL of $CDCl_3$ and shaken with 0.8 mL of D_2O containing 6 mol (relative to the cyclic ether) each of KSCN and either α-phenylethylammonium bromide or the hydrobromide of methyl α-phenylglycinate. The organic layer was separated and dried with magnesium sulfate, and the 100-MHz ^1H NMR spectrum was examined.

The relative amounts of cyclic ether and complexed salt were determined (±5%) by integration of appropriate ^1H NMR peaks of the host and guest entities. In parallel runs made without host present, or alternatively without the KCN present, peaks due to the salts were absent from the $CDCl_3$ layer's spectra. Table II records the results.

Extraction into Carbon Disulfide from Deuterated Water–Deuterated Methanol of Methanol by Complexation with (*R,R*)-70.[5] A 0.112 M solution of (*R,R*)-**70** in carbon disulfide (80 mg in 1.0 mL) was cooled to −78 °C and shaken with 1.5 mL of a 20% solution (by volume) of D_2O in CH_3OD which was 0.66 M in $LiPF_6$ (152 mg) at −78 °C. The layers were carefully separated at this temperature. Integrations of the ^1H NMR spectrum of the CS_2 layer taken (100 MHz) at 25 °C gave the relative amounts of CH_3OD [δ 3.18 (s, CH_3, 3 H)] and of (*R,R*)-**70** [δ 7.68 (m, $ArH^{4,5}$, 8), 7.00 (m, $ArH^{3,6,7,8}$, 12), 3.62 (m, $ArOCH_2$, 8), 3.00 (m, CH_2OCH_2, 8)].

Integrals	$ArH^{4,5}$	$ArH^{3,6,7,8}$	$ArOC-H_2$	$CH_2OC-H_2 + CH_3OD$
Calcd for 1:1 complex	75	150	75	103
Found	75	150	75	100

Repetition of the experiment except that the (*R,R*)-**70** was omitted gave no observable amount of CH_3OD in the CS_2 layer, although <10% of the observed in the original experiment would have been detected.

Preparation of Crystalline Host–Guest Complexes that Involve Amine Salts. Treatment of a solution of five-oxygen cycle **68**[4] (44.4 mg) in 2 mL of $CDCl_3$ with 46 mg of *tert*-butylammonium tetraphenylborate gave a clear solution, which after standing at 25 °C for 14 h deposited crystals: wt 75 mg (80%); mp 118–120 °C; ^1H NMR spectrum of this material in $DCCl_3$ indicated it to be 1:1. Anal. Calcd for $C_{56}H_{60}O_5NB$: C, 80.29; H, 7.17. Found: C, 80.30; H, 7.34.

A crystalline complex was formed by extracting 1.5 mL of a D_2O solution 4 M in $LiPF_6$ (pH 4.0) and 1.2 M in (*R*)-phenylglycine methyl ester hydrochloride with 3 mL of a 0.2 M solution of optically pure (*S,S*)-**70**[5] in $CDCl_3$ at −13 °C. The $CDCl_3$ layer was dried and its ^1H NMR spectrum showed it contained a 1:1 complex. After 0.5 h the complex crystallized and was collected and recrystallized from $CHCl_3$ to give 0.41 g (75%) of complex: phase change and bubbles 142–145 °C; mp 222–224 °C dec. The analysis and an X-ray molecular weight determination demonstrated that a 1:1 complex had formed and that 1 mol of $CHCl_3$ was present as solvate.[12] Anal. Calcd for $C_{57}H_{52}F_6NO_8P \cdot HCCl_3$: C, 60.93; H, 4.67; Cl, 9.30. Found: C, 60.75; H, 4.55; Cl, 8.91.

Preparation of Solid Host–Guest Complexes that Involve Metal Ions. A solution of 350 mg of amino ester **43** and 120 mg of KOH in 100 mL of methanol–water (9:1, v/v) was refluxed under N_2 for 6 h. The solution was evaporated (30 mm) and the residue was partitioned between 150 mL of water and 200 mL of ether. The ether layer was dried ($MgSO_4$), filtered, and evaporated to give <10 mg of material. The aqueous layer was extracted with four 100-mL portions of $CHCl_3$, which were combined, dried ($MgSO_4$), and evaporated to give 50 mg of material. The ^1H NMR spectrum (60 MHz) of this substance in $CDCl_3$ gave signals indicative of complexed material: δ 6.98–8.18 (complex m, ArH, 10), 4.98 (ABq, $ArCH_2O$, 2), 4.20 (s br, OCH_2CO, 2), 2.85–4.15 (m, OCH_2CH_2O, $ArCH_2N$ and OCH_2CH_2N, 26) and 2.40–2.70 (m, NCH_2CH_2O, 4). A 30-mL portion of the above aqueous solution was brought to pH 1 with 6 N hydrochloric acid and continuously extracted with $CHCl_3$ for 8 h. The $CHCl_3$ extract was dried ($MgSO_4$), filtered, and evaporated to dryness to give a powder. A 70-eV mass spectrum of the residue (40 mg) showed a parent M^+ 713 (potassium salt of host amino acid), but no peak at 675 (molecular ion of amino acid **50**). The hydrochloride, potassium salt of the amino acid was apparently extracted into $CHCl_3$. Neutralization of amino acid **50** with KOH gave the potassium salt of the amino acid as a powder (**71**). Anal. Calcd for $C_{38}H_{44}O_{10}NK$: C, 63.94; H, 6.22; K, 5.49. Found: C, 62.21; H, 6.12; K. 5.64.

A solution of 3.5 g of amino ester **43** and 3.2 g of $Ba(OH)_2 \cdot 8H_2O$ in 400 mL of methanol–water (4:1, v/v) under N_2 was refluxed for 8 h. The solution was concentrated (30 mm) to 40 mL and 300 mL of water and 75 mL of acetic acid were added to the mixture. The aqueous solution was extracted three times with 300-mL portions of $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated to 40 mL. The crude product was chromatographed on 200 g of silica gel made up in benzene. Elution of the column with up to 1:4 (v/v) 2-propanol–ether mixture gave only traces of material. Elution of the column with 3 L of methanol–ether (1:4) and 2 L of methanol–ether (2:3, v/v) gave 1.5 g (40%) of the barium salt of amino acid **50** as a powder (**79**). The 1:2 complex is readily soluble in water, methanol, $CHCl_3$, and acetic acid, which demonstrates its mixed hydrophilic–lipophilic character: 100-MHz ^1H NMR ($CDCl_3$) δ 6.90–8.20 (complex m, ArH, 10), 4.82 (ABq, J_{AB} = 7 Hz, $ArCH_2O$, 2), 4.72 (s br, OCH_2CO_2, 2), 2.85–4.10 (m, OCH_2, $ArCH_2N$, 24) and 2.80 (m, NCH_2CH_2O, 4). The spectrum is dramatically different from that of the uncomplexed amino acid hydrochloride. Anal. Calcd for $C_{76}H_{88}O_{20}N_2Ba$: C, 61.37; H, 5.92; Ba, 9.24. Found: C, 61.98; H, 6.10; Ba, 9.58.

A solution of this complex in methanol–water was acidified with 5% sulfuric acid. No precipitate of $BaSO_4$ was formed.

The alkaline earth metal complexes of the diacids containing one dinaphthyl unit and five, six, or seven oxygens (macrocycles **45, 44,** and **46,** respectively) were prepared by a method illustrated as follows. A solution of 0.70 g (1 mmol) of methyl ester **38** and 2 mmol of $M(OH)_2$ (M = Ca, Sr, or Ba) in 200 mL of methanol–water (4:1) was refluxed under N_2 for 8 h. The solution was concentrated to about 20 mL and 150 mL of water was added. The aqueous solution was extracted with two 50-mL portions of CH_2Cl_2 to remove neutral material. The water layer was then extracted with five 100-mL $CHCl_3$–methanol (3:1) portions to give $CHCl_3$ solutions of the salts. The combined organic extracts were dried with the metal sulfates corresponding to the $M(OH)_2$ used in the hydrolysis. The dried solutions were evaporated to give the metal salt complexes as white powders. Since $BaSO_4$ was an inefficient drying agent, benzene was added during the evaporation to help dry the solution when M = Ba. The yields of the salts ranged from 80% for Ca and Sr to ~50% for Ba. The extraction of the barium salt was considerably less efficient than for the other two ions. The ^1H NMR spectra (60 MHz) of the salts in CD_3CO_2D were consistent with highly complexed macrocyclic ether structures with the differences for the three complexes not significant enough to correlate with possible metal positioning within the macrocycle. The ^1H NMR spectrum (60 MHz) of the barium salt **76** in CD_3CO_2D gave δ 7.00–8.20 (complex m, ArH, 10), 4.98 (ABq, J_{AB} = 12 Hz, $ArCH_2$, 4), 4.38 (s br, OCH_2CO_2, 4), and 2.95–4.20 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Ba$: C, 54.04; H, 4.80; Ba, 17.16. Found: C, 53.68; H, 4.77; Ba, 15.47.

The ^1H NMR spectrum (60 MHz) for the strontium salt **75** in CD_3CO_2D gave δ 7.08–8.22 (complex m, ArH, 10), 5.04 (ABq, J_{AB} = 13 Hz, 4), 4.42 (s br, OCH_2CO_2, 4), and 2.90–4.05 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Sr$: C, 57.63; H, 5.10; Sr, 11.68. Found: C, 57.33; H, 5.84; Sr, 10.88.

The ^1H NMR spectrum (60 MHz) for the Ca salt **74** in CD_3CO_2D gave δ 7.10–8.18 (complex m, ArH, 10), 4.80 (ABq, J_{AB} = 12 Hz, $ArCH_2$, 4), 4.22 (br s, OCH_2CO_2, 4), and 2.90–4.20 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Ca$: C, 61.52; H, 5.45. Found: C, 62.04; H, 6.03.

Application of this same method to diester **39** and calcium hydroxide produced calcium salt **77** (~80%). Anal. Calcd for $C_{34}H_{34}O_{11}Ca$: C, 61.98; H, 5.21. Found: C, 60.81; H, 5.54.

Application of this same method to diester **40** and barium hydroxide gave barium salt **78** (~75%). Anal. Calcd for $C_{38}H_{42}O_{13}Ba$: C, 54.07; H, 5.02; Ba, 16.27. Found: C, 53.89; H, 5.20; Ba, 16.04.

Application of this method to diester **38** and a 10 mmol of $Ba(OH)_2$ which was 0.8% $Sr(OH)_2$ gave a solution which after hydrolysis and the CH_2Cl_2 wash was acidified with excess acetic acid. The solution was extracted by the above method, dried with $MgSO_4$, and evaporated to a gum. The mass spectrum of this material contained M^+ of both diacid **44** at M^+ 664, and more interestingly, that of the strontium salt **75** at M^+ 750. Thus diacid **44** scavenged strontium from bulk barium, and the strontium was carried through the acidification and

Table VI. Distribution Ratios (q_A or q'_A)[c] for Carboxylate Ligands from Hosts 48 and 47 between Organic Phases and Aqueous Solutions of Metal Hydroxides–Lithium Hydroxides at Ambient Temperature

Run no.	Organic phase		Aqueous Phase						[Ligand] × 10^5 M at equilibrium		q_A for Na^+ or K^+, and q'_A for Ca^{2+}[a]
			Ligand		Metal compd						
	Kind	Vol, mL	Kind	Concn, M	Vol, mL	Kind	Concn, M	LiOH concn, M	Organic phase	Water phase	
1	CH_2Cl_2	5	**48**	0.00010	10	NaOH	0.010	0.0010	9.18	5.47	1.68
2	CH_2Cl_2	5	**48**	0.00010	10	KOH	0.010	0.0010	3.47	7.36	0.47
3[b]	CH_2Cl_2	3	**48**	0.00010	10	$Ca(OH)_2$	0.010	0.0010	24.5	3.24	3.77 ± 0.04
4[b]	CH_2Cl_2	3	**48**	0.00010	10	$Ba(OH)_2$	0.010	0.0010	23.7	3.23	2.3 ± 0.1
5[b]	CH_2Cl_2	10	**47**	0.00010	10	NaOH	0.010	0.0010	10.2	1.07	9.5 ± 0.6
6[b]	CH_2Cl_2	10	**47**	0.00010	10	KOH	0.010	0.0010	10.6	0.299	35.6 ± 0.8
7[b]	CH_2Cl_2	3	**47**	0.00010	10	$Ca(OH)_2$	0.010	0.0010	22.8	3.16	3.6 ± 0.2
8[b]	CH_2Cl_2	3	**47**	0.00010	10	$Ba(OH)_2$	0.010	0.0010	21.9	4.10	2.67 ± 0.02
9	$C_6H_5CH_3$	110	**48**	0.0020	5	LiCl	0.50	0.0043	0.098	99.2	9.9×10^{-4}
10	$C_6H_5CH_3$	110	**48**	0.0020	5	NaCl	0.50	0.0043	0.266	94.5	2.8×10^{-3}
11[c]	$C_6H_5CH_3$	110	**48**	0.0020	5	NaCl	0.50	0.0043	0.241	94.5	2.5×10^{-3}
12[c]	$C_6H_5CH_3$	110	**48**	0.0020	5	KCl	0.50	0.0043	0.174	94.4	1.8×10^{-3}
13	$C_6H_5CH_3$	20	**48**	0.0020	5	$CaCl_2$	0.50	0.0043	22.6	13.1	8.6×10^{-1}
14	$C_6H_5CH_3$	110	**47**	0.0020	5	LiCl	0.50	0.0043	0.197	102	1.9×10^{-3}
15	$C_6H_5CH_3$	110	**47**	0.0020	5	NaCl	0.50	0.0043	1.03	81.7	1.2×10^{-2}
16[c]	$C_6H_5CH_3$	110	**47**	0.0020	5	NaCl	0.50	0.0043	0.954	83.0	1.1×10^{-2}
17[c]	$C_6H_5CH_3$	110	**47**	0.0020	5	KCl	0.50	0.0043	0.602	80.6	7.4×10^{-3}
18	$C_6H_5CH_3$	20	**47**	0.0020	5	$CaCl_2$	0.50	0.0043	18.4	29.0	3.2×10^{-1}
19[d]	$C_6H_5CH_3$	21	**48**	0.00010	10	$CaCl_2$	0.95	0.0010	1.75	5.56	1.6×10^{-1}
20	$C_6H_5CH_3$	21	**48**	0.00010	10	$BaCl_2$	0.95	0.0010	0.0556	9.21	3.0×10^{-3}
21	$C_6H_5CH_3$	52	**47**	0.00010	10	$CaCl_2$	0.95	0.0010	0.625	8.12	3.8×10^{-2}
22[d]	$C_6H_5CH_3$	52	**47**	0.00010	10	$BaCl_2$	0.95	0.0010	0.0202	9.80	1.0×10^{-3}

[a] q_A values are reported for monovalent cations and $q'_A = q_A/2$ values for divalent cations. [b] Average values from two to four determinations. [c] The aqueous phases in these runs were initially 0.5 M in additional LiCl. [d] Average values of two determinations which were at least within 10% of one another.

extraction procedure.

Determination of the Lipophilizing Abilities of the Anions of Hosts 48 and 47 for Sodium, Potassium, Calcium, and Barium Cations. In these experiments, monocarboxylic acid hosts **48** and **47** were used to lipophilize Na^+, K^+, Ca^{2+}, and Ba^{2+} through salt complex formation. Aqueous solutions of these salts of **48** and **47** in conductivity water were prepared from reagent-grade metal hydroxide and analytically pure acid, and were extracted with spectral grade CH_2Cl_2. The stoichiometric composition of the extracted material was determined by its isolation and by measuring the amount of metal ion (by atomic absorption for Ca^{2+} and flame emission spectroscopy for Na^+ and K^+). The preparations of these salts and determinations of their compositions are first described.

All the equipment used for the preparation of the salts and for the metal determinations was washed with detergent, washed twice with dilute aqueous nitric acid, and rinsed five times with distilled water and five times with deionized water. All the glassware was made of borosilicate glass. Weighings of <10 mg were made with a Cahn balance. Compounds **48** or **47** (~10 mg) were completely dissolved in ~25 ml of ~0.020 M aqueous metal hydroxide solution. The aqueous solution was then extracted with three 50-mL portions of redistilled spectral quality CH_2Cl_2. The organic layers were separated after centrifugation, combined, and evaporated. The residual salt was dried at 165 °C in high vacuum for 24 h before use. The modifications involved in this procedure were for the calcium salts of **48** and **47** and the barium salt of **47**. In these preparations, **48** or **47** was first completely dissolved in 20 mL of ~0.01 M aqueous LiOH to which 20 mL of 0.5 M aqueous metal chloride was then added, and the aqueous solution was extracted as described. For each metal determination, blanks, samples, and standard solutions were run at least twice each and average values were obtained. All solutions were run as long as necessary to produce a stable reading (3–7 s). The wavelengths used for the determinations were 4226Å for Ca, 5890 Å for Na, and 7660 Å for K.

A PE-303 spectrophotometer was used for all the metal determinations. A calcium vapor lamp was used for the determination of calcium by atomic absorption and sodium and potassium were determined by air–acetylene flame emission. The salts used for the standards were reagent quality except for the calcium carbonate for the calcium standards (a primary standard). The solvent in which the determinations were made was reagent-grade DMF. For determination of sodium, a sample of 0.994 mg of the dried salt of **48** and 0.0916 mg of that of **47** was dissolved in DMF to give 10.00 mL of solution. Standards were prepared by dissolving 45.1 mg of NaBr in 100 mL of DMF. An aliquot of 25 mL was diluted to 250 mL to produce a solution that contained 10.08 μg/mL of Na. Aliquots (50 and 25 mL) of this solution were each diluted to 100 mL to produce three standard solutions. In determination of potassium, 1.280 mg of **48** and 0.906 mg of **47** as dried salts were each dissolved in DMF to give 10.00 mL of solution. For standards, 32.0 mg of KBr was dissolved in 100 mL of DMF. An aliquot of 25 mL of this solution was diluted with DMF to 250 mL to give a standard solution containing 10.5 μg/mL of K. Aliquots (50 and 25 mL) of this solution were each diluted to 100 mL to give two additional standard solutions of 5.20 and 2.65 μg/mL, respectively. In determination of calcium, the solution used for preparing both sample and standards was obtained by dissolving 5.85 g of lanthanum oxide in ~50 mL of aqueous hydrochloric acid and evaporating to dryness. The residue was dissolved in DMF and diluted to 500 mL with DMF. A sample of each of the calcium salts (0.830 mg and 1.587 mg of the salts of **48** and **47**, respectively) was dissolved quantitatively in the lanthanum-containing solution of DMF and diluted to 10.00 mL with the same solution. Calcium carbonate (14.6 mg) was dissolved in aqueous hydrochloric acid and the solution was evaporated to dryness. The residue was diluted with the same lanthanum solution to 100 mL to give a solution containing 58.5 μg/mL of calcium and 10 000 μg/mL of lanthanum. Further dilution as before gave additional standard solutions containing 5.85 and 2.92 μg/mL of calcium (respectively) and 10 000 μg/mL of lanthanum.

In the analyses for all three metals, the metal content of the samples was between 3 and 6 μg/mL and the standards had metal contents that ranged higher and lower than the unknowns. A calibration curve of absorbance vs. μg/mL was plotted for each metal, which was linear for Ca and nearly so for Na and K. The concentration of metal in the unknown samples was then read from the calibration curve. Unfortunately, these methods could not be applied to Ba due to this element's low sensitivity when an acetylene–air flame is used. The results for the other salts are as follows. Anal. for the Na salt of **48**. Calcd for $C_{31}H_{31}NaO_8$: Na, 4.14. Found: Na, 3.90. Anal. for the K salt of **48**. Calcd for $C_{31}H_{31}KO_8$: K, 6.85. Found: K, 6.42. Anal. for the Ca salt of **48**. Calcd for $C_{62}H_{62}CaO_{16}$: Ca, 3.63. Found: Ca, 3.80. Anal. for the Na salt of **47**. Calcd for $C_{33}H_{35}NaO_9$: Na, 3.84. Found: Na, 3.60. Anal. for the K salt of **47**. Calcd for $C_{33}H_{35}KO_9$: K, 6.36. Found: K, 5.98. Anal. for the Ca salt of **47**. Calcd for $C_{66}H_{70}CaO_{18}$: Ca, 3.36. Found: Ca, 3.53.

The salt distribution experiments between water and CH_2Cl_2 were carried out with UV spectra (Cary Model 14 spectrometer) as an an-

alytical probe. Spectral-grade solvents and analytically pure **48** and **47** were used. Extinction coefficients for the metal salts of **48** and **47** (see above) in CH_2Cl_2 and water at about 10^{-4} M concentration were determined at their λ_{max} of 337, 324, 294, 286, and 276 nm. All extraction experiments were performed by the following procedure. Table VI reports the volumes and concentrations. All measuring and transferring of solutions was done with volumetric pipettes and flasks.

An accurately weighed sample (~10 mg) of host **48** or **47** was dissolved in enough of the appropriate standardized metal hydroxide solution (~10^{-2} to 10^{-3} N) to give 10.00 mL of solution. Measured aliquots of this solution were mixed (in pear-shaped separatory funnels or in flasks fitted with magnetic stirrers and stoppers) with appropriately measured aliquots of aqueous metal chloride or hydroxide solutions and with measured aliquots of the organic solvent. The separatory funnels were shaken 200–300 times, or the flasks' contents were stirred for ~12 h. In either method, after centrifugation the layers were separated and their UV spectra were determined. The aqueous phases were measured directly using cells with appropriate pathlengths (1 or 0.1 cm). For the organic phases, where the solvent was CH_2Cl_2, the UV spectra were obtained directly on the solutions or by suitable dilution with the same solvent of measured aliquots of the solutions. Cells of appropriate pathlengths (0.1, 1, 2, or 4 cm) were employed. For organic phases where the solvent was not CH_2Cl_2, a measured aliquot was evaporated to dryness under vacuum. The residue was transferred quantitatively with CH_2Cl_2 to a volumetric flask and diluted with CH_2Cl_2 to the mark. The UV spectra of both the aqueous and CH_2Cl_2 solutions were recorded at about 10^{-4} M concentrations of carboxylate ligand. The concentrations of that ligand in both layers were calculated from the extinction coefficients of the unknowns as compared to those of the known salt solutions at the five λ_{max} wavelengths. The concentrations recorded in Table VI represent the average values calculated at different wave lengths. The barium salt was assumed to have the composition $C_{66}H_{70}BaO_{18}$.

Registry No.—**3,** 602-09-5; **4,** 55441-94-6; **5,** 55441-97-9; **6,** 55441-98-0; **7,** 55441-99-1; (+)-**8,** 55515-95-2; (*S*)-(−)-**8,** 42167-06-6; (*R*)-(+)-**8,** 42167-07-7; (+)-**9,** 55442-32-5; **9** triacetate, 65942-49-6; **10,** 55442-35-8; **11,** 55442-31-4; **12,** 55442-26-7; **13,** 55442-28-9; **14,** 55442-03-0; **15,** 55442-04-1; **16,** 55442-91-6; **17,** 55442-90-5; **18,** 55442-92-7; **20,** 55442-88-1; **21,** 55442-89-2; **22,** 55442-93-8; **23,** 55442-94-9; (±)-**24,** 55442-95-0; (*S*)-(−)-**24,** 65981-87-5; (*R*)-(+)-**24,** 65981-88-6; (±)-**25,** 55442-96-1; (*S*)-(−)-**25,** 65981-85-3; (±)-**26,** 55442-97-2; (*R*)-(−)-**26,** 65981-86-4; **27,** 55442-98-3; **28,** 55442-99-4; (±)-**29,** 55442-40-5; (*S*)-(−)-**29,** 55516-00-2; (±)-**30,** 55516-03-5; (*S*)-(−)-**30,** 55442-50-7; (±)-**31,** 55516-06-8; (*R*)-(−)-**31,** 55442-52-9; **32,** 55500-30-6; **33,** 55442-43-8; **34,** 55442-59-6; **35,** 55442-47-2; **36,** 55442-41-6; **37,** 55442-42-7; (±)-**38,** 55516-01-3; (*S*)-(−)-**38,** 42167-09-9; (±)-**39,** 55516-04-6; (*S*)-(−)-**39,** 55442-51-8; (±)-**40,** 55516-07-9; (*R*)-(−)-**40,** 55442-53-0; **41,** 55442-44-9; **42,** 65942-48-5; **43,** 55442-48-3; (±)-**44,** 55516-02-4; (*S*)-(−)-**44,** 42167-01-1; (±)-**45,** 55516-05-7; (*S*)-(−)-**45,** 42167-02-2; (±)-**46,** 55516-08-0; (*R*)-(−)-**46,** 42167-03-3; **47,** 55442-45-0; **47** Na Salt, 65943-28-4; **47** Ca Salt, 65995-88-2; **47** K Salt, 65943-29-5; **48,** 55442-46-1; **48** Na Salt, 65943-26-2; **48** K salt, 65943-27-3; **48** Ca salt, 65995-87-1; **49,** 55442-60-9; **49** methyl ester, 55442-65-4; **50,** 55442-49-4; (±)-**51,** 55529-01-6; (*R*)-(±)-**51,** 55442-61-0; **51** methyl ester, 55516-13-7; (±)-**52,** 55442-54-1; (*S*)-(−)-**52;** 55516-09-1; (±)-**53,** 55442-55-2; (*S*(−(+)-**53,** 55516-10-4; (±)-**54,** 55442-56-3; (*S*)-(−)-**54,** 55516-11-5; **55,** 55442-57-4; (±)-**55** tetramethyl ester, 55500-31-7; (*S*)-(−)-**55** tetramethyl ester, 55821-99-3; (±)-**56,** 55442-58-5; (*S*)-(−)-**56,** 55516-12-6; **57,** 63783-48-2; **58,** 55442-72-3; **59,** 55442-73-4; **60,** 55442-75-6; **61,** 55442-76-7; **62,** 55442-77-8; **63,** 55442-80-3; **64,** 55442-82-5; **64** tetraacetate, 55442-81-4; **65,** 55442-85-8; **65** dimethyl ester, 55442-84-7; **66,** 55442-83-6; **67,** 55824-36-7; **68,** 55515-78-1; **68** *t*-$BuNH_3$·BPh_4 complex salt, 66070-44-8; (*R,R*)-**70,** 41024-95-7; (*S,S*)-**70,** 41024-93-5; (*S,S*)-**70** methyl *R*-phenylglycinate PF_6 complex salt, 66070-43-7; **71,** 55522-34-4; **74,** 55522-35-5; **75,** 55522-33-3; **76,** 55522-32-2; **77,** 55522-36-6; **78,** 65969-59-7; **79,** 65995-86-0; *N*-butoxymethylmorpholine, 5625-84-3; 3-morpholine-2,2′-dihydroxy-1,1-dinaphthyl hydrochloride, 65942-46-3; 3-morpholino-2,2′-dihydroxy-1,1-dinaphthyl, 65942-47-4; 1,2-ethanedithiol, 540-63-6; 1,2-disulfhydrylbenzene, 17534-15-5; 2-sulfhydrylphenol, 1121-24-0; 8,9-benzo-1,16-ditosyl-1,4,1,10,13,16-hexoxohexadeca-8-ene, 41024-87-7; 3-allylcatechol, 1125-74-2; 4-(3′-hydroxypropyl)catechol, 46118-02-9; 4 allylveratrole, 93-15-2; 2,3:5,6-dinaphtho-13,14-(3-allyl-1,2-benzo)1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene, 55442-87-0; 3-(3,4-dimethoxyphenyl)-1-propanol, 3929-47-3; 3-(3,4-dimethoxyphenyl)-2-propanol, 19578-92-8; 2,3:4,5-Dinaphtho-13,14-(3-aminomethyl-1,2-benzo)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene, 65942-45-2; pentaethylene glycolditosylate, 41024-91-3; thioglycolic acid, 68-11-1; β-sulfhydrylpropionic acid, 107-96-0; dimethyl malonate, 108-59-8; (R)-phenylglycine methyl ester hydrochloride, 19883-41-1.

References and Notes

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Carbon-13 NMR Study of the Effect of the Polar Character of Substituents on p–π Conjugation in α,β-Unsaturated Ethers, Acetals, Orthoesters, and Orthocarbonates

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^{13}C NMR chemical shifts have been measured for a number of α,β-unsaturated (olefinic) ethers, acetals, orthoesters, and orthocarbonates. The results indicate that in a system ROC=C the polar character of R has a definite effect on the extent of p–π conjugation in the vinyloxy group: electron-releasing substituents R increase p–π conjugation, and vice versa. This can be inferred from the effect of R on the ^{13}C chemical shifts of the olefinic carbons: with increasing electron-releasing nature of R the α-carbon signals move downfield and the β-carbon signals upfield, suggesting enhanced conjugation. The shift values appear to be approximately linear functions of the Taft σ^* value for the group R, provided that the chemical shifts are not significantly affected by conformational changes or the through-space shielding effects of R. As an example, the α- and β-carbon ^{13}C chemical shifts ($CDCl_3$, internal Me_4Si) of 2-substituted 4-methylene-1,3-dioxolanes may be expressed as follows: δ (C-α)/ppm = (156.60 ± 0.12) − (0.76 ± 0.09)$\Sigma\sigma^*_R$ and δ (C-β)/ppm = (77.27 ± 0.10) + (1.12 ± 0.09)$\Sigma\sigma^*_R$, in which the term $\Sigma\sigma^*_R$ represents the sum of the σ^* values for the two groups attached to C-2.

Alkyl vinyl ethers ($ROCH{=}CH_2$) are characterized by a high degree of p–π conjugation in the vinyloxy group, which may be described by the canonical structures I and II.

I II

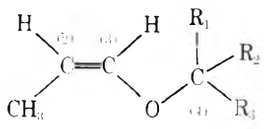
Evidence of the reality of this kind of electron delocalization in vinyl ethers is provided by several facts. For example, thermochemical studies[1] suggest a conjugation energy of ca. 15 kJ mol^{-1} for ethyl vinyl ether. Moreover, according to the canonical form II one might expect the presence of excessive negative charge on the β carbon (C-β) of the vinyl group, which is confirmed by both ^{13}C and ^1H NMR spectroscopy: the C-β atom of methyl vinyl ether is shielded by ca. 37 ppm relative to the C atoms of ethylene and the protons of the terminal methylene group by ca. 1.4 ppm relative to the protons of ethylene.[2,3]

Besides the excessive negative charge on C-β, there is also an excess of positive charge on the ethereal oxygen atom in II. Thus it appears that the polar nature of the group R, directly bound to the O atom, could have a significant effect on the stability of this mesomeric form and thereby also on the extent of conjugation, which should increase with increasing electropositive (electron releasing) nature of R. The main purpose of the present work was to seek the possible relation between the polar character of R and the extent of p–π conjugation as measured by the ^{13}C NMR chemical shift of the C-β atom in the following α,β-unsaturated ethers, acetals, orthoesters, and orthocarbonates.

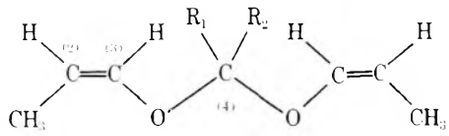
For a related study involving substituent effects on the olefinic carbon shifts in 4-substituted phenyl vinyl ethers, sulfides, and selenides, see ref 4, and for a treatment of substituent electronic effects on π systems see ref 5.

Results and Discussion

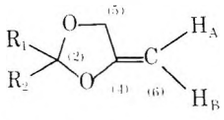
The following reasons make structure **3** almost ideal for studying the effect of the polar nature of R_1 and R_2 on p–π conjugation. First, the extent of conjugation is also affected by the degree of p–π overlapping in the vinyloxy system, which depends on the relative spatial orientation of the respective orbitals. In **3**, the ring conformation and hence the degree of p–π overlap are not likely to be significantly dependent on R_1 and R_2. In addition, the through-space effects of these groups on the ^{13}C chemical shift of C-β are assumingly small because of the long distance between these moieties. Figure 1 shows

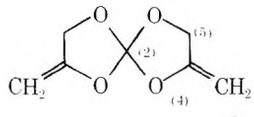


1a, $R_1 = R_2 = H$; $R_3 = OMe$
b, $R_1 = H$; $R_2 = Me$; $R_3 = OMe$
c, $R_1 = R_2 = Me$; $R_3 = OMe$
d, $R_1 = R_2 = H$; $R_3 = OCH{=}CH_2$
e, $R_1 = H$; $R_2 = Me$; $R_3 = OCH{=}CH_2$
f, $R_1 = H$; $R_2 = R_3 = OMe$
g, $R_1 = Me$; $R_2 = R_3 = OMe$
h, $R_1 = R_2 = H$; $R_3 = MeOCH_2$



2a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = H$; $R_2 = i$-Pr
d, $R_1 = H$; $R_2 = t$-Bu
e, $R_1 = H$; $R_2 = C(Me){=}CH_2$
f, $R_1 = R_2 = Me$
g, $R_1R_2C<$ = 
h, $R_1 = Me$; $R_2 = i$-Pr
i, $R_1 = H$; $R_2 = OMe$
j, $R_1 = Me$; $R_2 = OMe$
k, $R_1 = H$; $R_2 = OCH{=}CHMe$ (*Z*)
l, $R_1 = Me$; $R_2 = OCH{=}CHMe$ (*Z*)





4

3a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = H$; $R_2 = i$-Pr
d, $R_1 = H$; $R_2 = t$-Bu
e, $R_1 = H$; $R_2 = Ph$
f, $R_1 = R_2 = Me$
g, $R_1 = Me$; $R_2 = i$-Pr
h, $R_1 = Me$; $R_2 = t$-Bu
i, $R_1 = H$; $R_2 = OMe$
j, $R_1 = H$; $R_2 = OEt$
k, $R_1 = H$; $R_2 = OCH{=}CH_2$
l, $R_1 = Me$; $R_2 = OMe$
m, $R_1 = R_2 = OMe$

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Table I. ^{13}C NMR Chemical Shift Data ($CDCl_3$ as Solvent, δ Values in ppm from Internal Me_4Si) for the Compounds Studied in This Work

Compd	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
1a	62322-39-8	9.18	103.07	143.02	96.24			55.47
b	62322-40-1	9.25	102.51	140.58	101.54			53.73 (MeO), 19.97 (Me)
c	62322-41-2	9.30	102.86	137.99	104.16			48.85 (MeO), 24.85 (Me)
d	66291-04-1	9.26	104.61	142.62	93.40			149.28 (C-α), 91.69 (C-β)
e	66291-05-2	9.33	104.30	140.33	99.83			147.63 (C-α), 91.88 (C-β), 20.13 (Me)
f	66178-20-9	9.26	104.12	137.99	113.54			51.49
g	66178-22-1	9.34	103.80	137.66	115.33			49.79 (MeO), 20.14 (Me)
h	62322-42-3	9.26	101.44	145.78	71.31			59.05 (MeO), 71.31 (CH_2)
2a	62322-33-2	9.26	104.28	142.70	94.54			
b	62322-34-3	9.33	103.89	140.58	100.40			20.21
c	62322-35-4	9.36	103.52	141.93	108.31			32.63 (CH), 17.33 (Me)
d	62322-36-5	9.44	102.86	143.88	111.17			36.62 (C), 24.74 (Me)
e	66291-06-3	9.33	103.89	140.58	103.24			140.82 (C), 114.60 (CH_2), 17.45 (Me)
f	62322-38-7	9.34	104.20	137.75	101.93			25.66
g	62322-37-6	9.34	104.36	138.64	113.13			36.06, 23.47
h	66270-87-9	9.34	103.88	137.34	106.23			35.17 (CH), 18.19 (Me), 17.30 (2 Me)
i	66323-51-1	9.34	105.10	137.82	112.48			51.74
j	66178-25-4	9.33	104.70	137.17	115.17			51.54 (MeO), 21.51 (Me)
k	66291-07-4	9.34	106.07	137.50	111.27			See (C-1)–(C-3)
l	66178-27-6	9.34	105.66	136.93	114.92			22.50 (Me); see (C-1)–(C-3)
3a	4362-24-7		97.06		155.69	66.76	78.37	
b	14738-99-9		104.33		156.58	67.55	77.96	19.69
c	66290-92-4		110.70		156.50	67.49	77.48	32.08 (CH), 16.32 (Me)
d	66290-93-5		112.57		156.67	67.74	77.24	34.60 (C), 23.88 (Me)
e	4362-26-9		105.96		156.25	67.62	78.61	136.56, 130.05, 128.66, 126.79
f	19358-05-5		111.92		156.26	66.44	77.64	25.10
g	66290-94-6		115.89		156.50	66.76	77.16	36.14 (CH), 19.90 (Me), 17.14 (2 Me)
h	66290-95-7		117.60		156.91	67.25	76.75	38.98 (C), 24.93 (3 Me), 19.09 (Me)
i	66290-96-8		117.10		154.95	66.08	79.59	51.03
j	66290-99-1		116.47		154.72	65.79	79.43	60.02 (CH_2), 15.03 (Me)
k	66291-00-7		115.08		153.90	65.54	80.73	144.97 (CH), 93.81 (CH_2)
l	66291-01-8		124.02		155.37	67.33	78.46	49.38 (MeO), 22.58 (Me)
m	66291-02-9		135.55		154.64	65.95	79.51	51.00
4	66290-97-9		135.82		152.58	67.55	81.54	

the ^{13}C chemical shift of C-β in **3** (from Table I) as a function of the sum of the Taft's polar substituent constants[6] for R_1 and R_2. Compound **3k** was not included in the plot, because the value of the σ* constant for a vinyloxy group was not known. Excluding the point for **3m** ($R_1 = R_2 = OMe$), the relation between δ(C-β) and $\Sigma\sigma^*_R$ appears linear and a least-squares treatment of δ(C-β) against $\Sigma\sigma^*_R$ gives

$$\delta(\text{C-}\beta)/\text{ppm} = (77.27 \pm 0.10) + (1.12 \pm 0.09)\Sigma\sigma^*_R \quad (1)$$

with a correlation coefficient of $r = 0.969$. The shift value for C-β of **3m** is ca. 1 ppm to higher field than predicted by the above equation, for no obvious reason.

On the other hand, using the ^1H NMR shift values for the olefinic protons in **3** (Table II), the following equations are obtained (the compounds included are **3a–j, 3l,** and **3m**):

$$\delta(H_A)/\text{ppm} = (3.76 \pm 0.02) + (0.057 \pm 0.015)\Sigma\sigma^*_R \quad (2)$$
$$(r = 0.76)$$

$$\delta(H_B)/\text{ppm} = (4.21 \pm 0.02) + (0.052 \pm 0.013)\Sigma\sigma^*_R \quad (3)$$
$$(r = 0.78)$$

Thus both the ^{13}C and ^1H NMR shift data confirm the expected effect of the polar nature of R_1 and R_2 on the extent of conjugation.

Although not revealed by the simple canonical forms I and II given above, MO calculations[7] suggest the presence of a slight excess of positive charge on the α carbon (C-α) of the vinyl group, in agreement with experimental evidence.[8] Thus the ^{13}C chemical shift of C-α should also be a function of the polar character of R, but changes in the latter should have opposite effects on the shift values of C-α and C-β. This view is confirmed by the plot of δ(C-α) H of **3** against $\Sigma\sigma^*_R$, shown in Figure 1. Once again, the relation appears linear and a least-squares treatment of the data (excluding **3k**) gives

$$\delta(\text{C-}\alpha)/\text{ppm} = (156.60 \pm 0.12) - (0.76 \pm 0.09)\Sigma\sigma^*_R \quad (4)$$

with $r = 0.931$.

The ^{13}C chemical shift for C-β in **3k** may now be used to estimate the σ* value of a vinyloxy group. By setting δ(C-β) = 80.73 ppm in eq 1, one obtains $\Sigma\sigma^*_R = 3.09$, from which $\sigma^*(CH_2{=}CHO) = 2.60$, since $\sigma^*_H = 0.49$.[6] Thus the vinyloxy group is considerably more electron withdrawing than the corresponding saturated group (CH_3CH_2O), for which σ* = 1.35.[6] This cannot be explained solely on the basis of the higher electron attracting character of the vinyl group (the σ* values of the vinyl and Et groups are 0.40 and −0.10,[6] respectively), but apparently a major contribution of the difference is due to the p–π conjugation in the vinyloxy group leading to a positively charged O atom, which strengthens its electron-attracting nature. As a check of the validity of the σ* value obtained, the ^{13}C chemical shift of C-β of **4** may be estimated as follows. Taking this compound as a derivative of **3** with the polar characters of the groups (R_1 and R_2) attached to the central carbon corresponding to those of an EtO and a vinyloxy group ($\Sigma\sigma^*_R = 1.35 + 2.60 = 3.95$), one calculates from eq 1 δ(C-β) = 81.69 ppm for **4**, not far from the experimental value of 81.54 ppm.

Although it seems likely that R_1 and R_2 cannot significantly affect the ring conformation of **3**, the size and nature of the groups R_1–R_3 in **1** may markedly influence on the prevailing rotamer about the O–C(sp^2) bond. For $R_1 = R_2 = R_3 = H$, the most probable structure is the planar *s*-trans form,[9–12] whereas

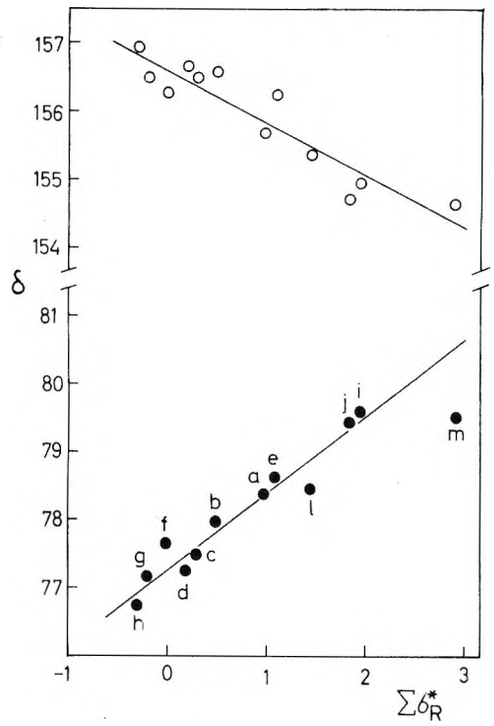

Figure 1. The values of δ(C-α) (○) and δ(C-β) (●) of 2-substituted 4-methylene-1,3-dioxolanes (**3**) as a function of $\Sigma\sigma^*_R$.

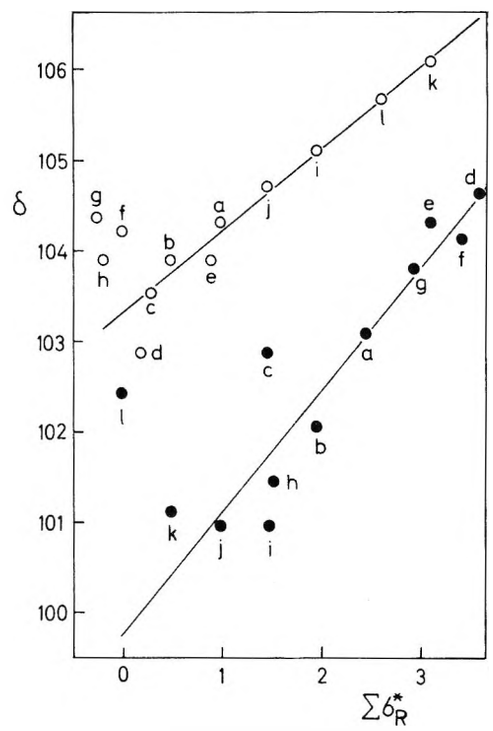

Figure 2. The values of δ(C-β) of **1** (●) and **2** (○) as a function of $\Sigma\sigma^*_R$.

this structure is less easily achieved if the substituents are bulkier. The present data supplemented by some previous results allow us to study the nature of the predominant rotamer in **1** in detail. In Figure 2, a plot of the ^{13}C chemical shift of C-β in **1** against $\Sigma\sigma^*_R$ is represented. The shift data for **1i** ($R_1 = R_2 = R_3 = H$), **1j** ($R_1 = R_2 = H$, $R_3 = Me$), **1k** ($R_1 = R_2 = Me$, $R_3 = H$), and **1l** ($R_1 = R_2 = R_3 = Me$) are from ref 12, and the σ^* value of the vinyloxy group has been taken as determined above. Excluding the points for **1c** and **1l**, the relation between δ(C-β) and $\Sigma\sigma^*_R$ appears linear, a least-squares treatment of the data giving

$$\delta(\text{C-}\beta)/\text{ppm} = (99.76 \pm 0.32) + (1.34 \pm 0.14)\Sigma\sigma^*_R \quad (5)$$

with $r = 0.962$. Thus the sensitivity of p–π conjugation in **1** to changes in the polar character of the group bound to the O atom of the vinyloxy group is practically equal to that in **3** (the slope values are not far from each other). The shift value for **1i** ($R_1 = R_2 = R_3 = H$) is slightly lower than expected from the above equation, which points to a very small deviation from the fully planar *s*-trans form for the other compounds used in the derivation of eq 5, if it is accepted that **1i** is completely planar. Compounds **1c** ($R_1 = R_2 = Me$; $R_3 = OMe$) and **1l** ($R_1 = R_2 = R_3 = Me$) are definitely nonplanar and possibly **1k** ($R_1 = R_2 = Me$; $R_3 = H$), too, but even in these compounds the deviation from the planar *s*-trans form must be small, since previous ^{13}C NMR studies[13] have shown that for a nonplanar gauche form δ(C-β) can be at least 15 ppm higher than expected for the planar form. Interestingly, the point for **1g** ($R_1 = Me$; $R_2 = R_3 = OMe$) falls on the line obtained, which suggests that steric repulsion between the H atom attached to C-α and the $R_1R_2R_3C$ group is less pronounced in **1g** than in **1c**, **1l**, and **1k**.

Included in Figure 2 there is also a corresponding plot of δ(C-β) vs. $\Sigma\sigma^*_R$ for **2** (the value of the $\Sigma\sigma^*_R$ term for **2g** was taken to be equal to twice the σ^* value of an *n*-Pr group, i.e., −0.26). If the points for **2d** and **2f–h** are excluded from a linear least-squares treatment of the data, one obtains

$$\delta(\text{C-}\beta)/\text{ppm} = (103.31 \pm 0.08) + (0.90 \pm 0.05)\Sigma\sigma^*_R \quad (6)$$

with $r = 0.993$. The higher than expected δ values for **2f–h** are a clear indication of the increased nonplanar character of these compounds, relative to the other members of the series. Thermodynamic studies[14,15] have suggested the planar *s*-trans, *s*-trans structure for these molecules, but the present more accurate results point to a minute deviation from full planarity for **2** and the majority of **1**. On the other hand, the ^{13}C chemical shift value for C-β of **2d** is slightly smaller than expected suggesting closer planarity, for no obvious reason. The slope value for **2** is smaller than that for **1**, which is reasonable in a qualitative sense, because in the former the polar effects of the substituents are distributed among two conjugating systems.

The α carbon chemical shifts of **1** and **2** are markedly affected by the through-space shielding effects of the substituents and hence the shifts cannot be used as a measure of p–π conjugation, contrary to the case in **3**.

Experimental Section

Materials. The preparation and properties of **1a–c, 1h, 2a–d, 2f,** and **2g** have been described in ref 14, those of **1f, 1g,** and **2i–l** in ref 15, and those of **3a** in ref 16.

Vinyl (*Z*)-Propenyl Formal (1d). Allyl 2-chloroethyl formal, bp 73 °C (18 Torr), was dehydrohalogenated and isomerized to **1d,** bp 118 °C (767 Torr), in a single step by treatment with an excess of KOBu-*t* in Me_2SO.

Acetaldehyde Vinyl (*Z*)-Propenyl Acetal (1e). Acetaldehyde allyl 2-chloroethyl acetal was prepared by acid-catalyzed addition of allyl alcohol to commercial 2-chloroethyl vinyl ether. Without isolation, the product was treated with KOH in triethanol amine to give acetaldehyde allyl vinyl acetal, which was isomerized to **1e,** bp 128–132 °C (764 Torr), by KOBu-*t* in Me_2SO.

Methacrolein Di((*Z*)-propenyl) Acetal (2e). Methacrolein diallyl acetal, bp 63 °C (10 Torr), was prepared from the aldehyde and triallyl orthoformate in allyl alcohol,[17] and the product was isomerized to **2e,** bp 66 °C (14 Torr), by KOBu-*t* in Me_2SO.

Methyl Isopropyl Ketone Di((*Z*)-propenyl) Acetal (2h), bp 84 °C (20 Torr), was prepared analogously from the corresponding diallyl acetal.

2-Substituted 4-Methylene-1,3-dioxolanes 3b–h. These compounds were obtained from the appropriate ketones and 3-chloro-1,2-propanediol, followed by dehydrohalogenation with KOH.[16] Bp's:

Table II. ^{1}H NMR Chemical Shift Data (δ Values in ppm from Internal Me_4Si) for 2-Substituted 4-Methylene-1,3-dioxolanes (3a–m)

Compd	H_A	H_B	CH_2	Other protons
3a[a]	3.88	4.33	4.33	5.18
b	3.84	4.27	4.27	5.22 (CH), 1.38 (Me)
c	3.75	4.20	4.35	4.87 (CH), ca. 1.8 (CH of the *i*-Pr group), 0.95 (2 Me)
d	3.74	4.20	4.36	4.78 (CH), 0.92 (3 Me)
e	3.90	4.30	4.30	5.95 (CH), 7.25 (aromatic protons)
f	3.77	4.23	4.48	1.42
g	3.67	4.12	4.37	1.27 (Me), 0.94 (2 Me)
h	3.74	4.23	4.50	1.30 (Me), 0.97 (3 Me)
i	3.88	4.35	4.46	5.88 (CH, 3.28 (MeO)
j	3.85	4.30	4.41	5.84 (CH), 3.54 (CH_2), 1.20 (Me)
k	4.00	4.40	4.49	6.13 (CH), 6.32, 4.63, and 4.20 (olefinic protons)
l	3.80	4.28	4.51	3.22 (MeO), 1.52 (Me)
m	3.88	4.32	4.44	3.27 (MeO)

[a] Reference 16.

2-methyl-4-methylene-1,3-dioxolane (3b) 97 °C (760 Torr), **2-isopropyl-4-methylene-1,3-dioxolane (3c)** 40 °C (20 Torr), **2-*tert*-butyl-4-methylene-1,3-dioxolane (3d)** 130 °C (760 Torr), **2-phenyl-4-methylene-1,3-dioxolane (3e)** 105 °C (10 Torr), **2,2-dimethyl-4-methylene-1,3-dioxolane (3f)** 106 °C (779 Torr), **2-methyl-2-isopropyl-4-methylene-1,3-dioxolane (3g)** 48 °C (20 Torr), and **2-methyl-2-*tert*-butyl-4-methylene-1,3-dioxolane (3h)** 86–88 °C (90 Torr).

2-Methoxy-4-methylene-1,3-dioxolane (3i). Equimolar amounts of $HC(OMe)_3$ and 3-chloro-1,2-propanediol were heated in a distillation apparatus in the presence of some *p*-toluenesulfonic acid until the evolution of MeOH ceased. The product was treated with KOH to give **3i**, bp 54 °C (60 Torr).

2-Ethoxy-, 2-Vinyloxy-, 2-Methyl-2-methoxy-, and 2,2-Dimethoxy-4-methylene-1,3-dioxolane (3j, 3k, 3l, and 3m, Respectively). See preparation of **3i**. Besides the diol, $HC(OEt)_3$, $HC(OCH_2CH_2Cl)_3$, $MeC(OMe)_3$, and $C(OMe)_4$ were used as the reagents (in the case of **3k**, the initial reaction product was 2-(2-chloroethyl)-4-chloromethyl-1,3-dioxolane, which required 2 molar equiv of KOH for dehydrochlorination to the final product). Bp's: **3j** 83 °C (97 Torr), **3k** 36–39 °C (9 Torr), **3l** ca. 65 °C (85 Torr), and **3m** 62 °C (6 Torr).

4,4′-Dimethylene-2,2′-spirobi-1,3-dioxolane (4), bp ca. 95 °C (23 Torr), was prepared from $C(OMe)_4$ and 2 molar equiv of 3-chloro-1,2-propanediol, followed by dehydrochlorination.

^{1}H NMR Spectra. The spectra were recorded at 60 MHz in CCl_4 (20%, v/v) with Me_4Si as internal standard. The chemical shifts are given in δ values (ppm) and the coupling constants in hertz. The spectra of **3a–m** are given in Table II. **1e:** 6.07 (H_α, J = 6.9), 4.46 (H_β), 1.55 (MeC=C), 6.34 (H'_α), 4.37 (H'_β, J = 13.7), 5.09 (H'_β, J = 6.9), 1.41 (**Me**CH, J = 5.3), 5.94 (CH). **2e:** 6.06 (H_α, J = 6.8), 4.45 (H_β), 1.56 (MeC=C, J_{vic} = 6.9, $J_{allylic}$ = 1.7), 5.06 (CH), 5.02 and 5.20 (olefinic protons), 1.73 (MeC=C). **4:** 3.97 and 4.43 (olefinic protons), 4.65 (CH_2).

^{13}C NMR Spectra. The spectra were recorded in $CDCl_3$ (20%, v/v) with Me_4Si as internal standard. For other details, see ref 13.

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Registry No.—Allyl 2-chloroethyl formal, 66291-03-0; acetaldehyde allyl vinyl acetal, 51914-88-6; methylacrolein diallyl acetal, 5187-69-9; methyl isopropyl ketone diallyl acetal, 66290-98-0; trimethoxymethane, 149-73-5; 3-chloro-1,2-propranediol, 96-24-2; tetramethoxymethane, 1850-142.

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Carbon-13 Nuclear Magnetic Resonance Spectra of Divinyl Ethers

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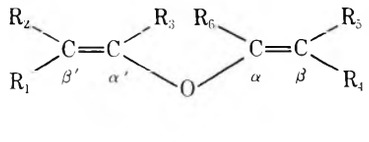
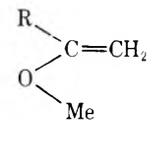
^{13}C NMR chemical shifts have been determined for a number of alkyl- and aryl-substituted divinyl ethers. On the basis of the shift data for the olefinic carbons it can be shown that alkyl substitution at one of the terminal (β) carbons of the divinyl ether skeleton leads to an enhanced conjugation between the O atom and the unsubstituted vinyl group, whereas there is a decrease in conjugation with the substituted vinyl group. This is likely to arise from the polar effect of the substituent, which opposes the accumulation of excessive negative charge (resulting from conjugation) on the substituted C atom. Thus the O atom conjugates more effectively with the other vinyl group. The results suggest further that unsubstituted or β- (β,β'-) substituted divinyl ethers have an essentially planar *s*-trans,s-trans structure, while α-substituted divinyl ethers have a slightly nonplanar *s*-cis,*s*-trans structure, and α,α'-substituted divinyl ethers are markedly nonplanar so that π–p–π conjugation is considerably weaker in these compounds than in the unsubstituted divinyl ether molecule.

In a previous paper,[1] the spatial structure of the divinyl ether skeleton in alkyl-substituted divinyl ethers (I) was discussed on the basis of thermodynamic data of isomeric interconversion. Interesting information was also obtained from ^{1}H NMR shift data, which revealed that alkyl substituents may have significant effects on charge distribution in



I



II

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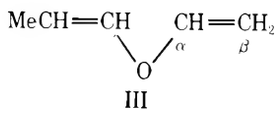
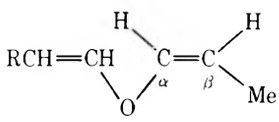
the divinyloxy system: substitution at C-β' increases electron density around C-β, but decreases it around C-β', whereas substitution at C-α' has a reverse effect. If it is assumed that in the unsubstituted divinyl ether molecule (I, R_1–R_6 = H) π–p–π conjugation between the lone pair electrons of the O atom and the π electrons of the C=C bonds is equally distributed between the two vinyl groups, the above findings suggest that alkyl substitution at C-β' decreases conjugation with the substituted vinyl group but increases conjugation with the unsubstituted vinyl group. These effects are reversed if substitution occurs at C-α'. The aim of the present work was to study these effects in more detail by ^{13}C NMR spectroscopy, which allows a direct "look" at the (C) atoms constituting the divinyl ether skeleton rather than just at atoms linked to it. The compounds investigated, together with their ^{13}C NMR chemical shift data, are given in Table I. For comparison, related data for some α-substituted methyl vinyl ethers (II) are also included in Table II.

Results and Discussion

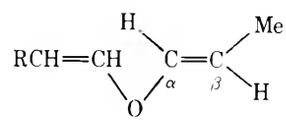
The data given in Table I enable us to evaluate the effects of the substituents attached to C-α' or C-β' on the ^{13}C chemical shifts of C-α and C-β. For example, the Me group of III



III



IV



V

leads to the following changes in the chemical shifts of C-α and C-β [the superscripts Me(Z) and Me(E) refer to the configurational position of the Me group in the propenyloxy system]:

$$\Delta(\text{C-}\alpha)^{\text{Me}(Z)} = +1.3 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Me}(Z)} = -2.7 \text{ ppm}$$

$$\Delta(\text{C-}\alpha)^{\text{Me}(E)} = +1.1 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Me}(E)} = -2.0 \text{ ppm}$$

Similarly, for IV one obtains

R = Me:

$$\Delta(\text{C-}\alpha)^{\text{Me}(Z)} = +2.4 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Me}(Z)} = -2.8 \text{ ppm}$$

$$\Delta(\text{C-}\alpha)^{\text{Me}(E)} = +1.1 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Me}(E)} = -2.8 \text{ ppm}$$

R = Et:

$$\Delta(\text{C-}\alpha)^{\text{Et}(Z)} = +2.4 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Et}(Z)} = -2.8 \text{ ppm}$$

R = i-Pr:

$$\Delta(\text{C-}\alpha)^{i\text{-Pr}(Z)} = +2.5 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{i\text{-Pr}(Z)} = -2.7 \text{ ppm}$$

$$\Delta(\text{C-}\alpha)^{i\text{-Pr}(E)} = +1.5 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{i\text{-Pr}(E)} = -1.6 \text{ ppm}$$

Further, for V one may calculate

R = Me:

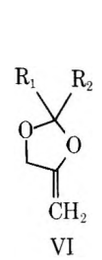
$$\Delta(\text{C-}\alpha)^{\text{Me}(Z)} = +2.4 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{\text{Me}(Z)} = -1.9 \text{ ppm}$$

R = i-Pr:

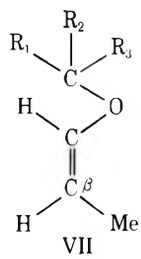
$$\Delta(\text{C-}\alpha)^{i\text{-Pr}(Z)} = +2.4 \text{ ppm}; \quad \Delta(\text{C-}\beta)^{i\text{-Pr}(Z)} = -3.2 \text{ ppm}$$

In **19** the combined effects of the two Me groups on δ(C-α) and δ(C-β) are calculated to be +2.4 and −3.5 ppm, respectively. In these examples, Δ(C-α) is always positive (+1.9 ppm on average for the β'-monoalkyl-substituted divinyl ethers) and Δ(C-β) always negative (−2.5 ppm on average). The increased shielding of C-β and decreased shielding of C-α point to an enhanced conjugation between the O atom and the (C-α)=(C-β) double bond, caused by alkyl substitution at C-β'. This effect is likely to arise from the higher electron-releasing character of the alkyl groups, relative to that of a hydrogen atom, which tends to oppose the accumulation of excessive negative charge on C-β', following from p–π conjugation:

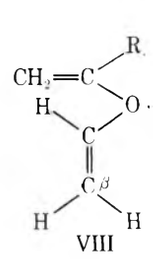
Thus it is easier for the O atom to conjugate more effectively with the other vinyl group. The effect of the polar nature of substituents on the extent of p–π conjugation has also been observed in other related systems; for example, in 2-substituted 4-methylene-1,3-dioxolanes (VI) the ^{13}C chemical shifts



VI



VII



VIII

of the olefinic carbons may be expressed by eq 1 and 2,[2] in which $\Sigma\sigma^*_R$ is the sum of the Taft's polar substituent constants for R_1 and R_2.

$$\delta(\text{C-}\alpha)/\text{ppm} = (156.60 \pm 0.12) - (0.76 \pm 0.09)\Sigma\sigma^*_R \quad (1)$$

$$\delta(\text{C-}\beta)/\text{ppm} = (77.27 \pm 0.10) + (1.12 \pm 0.09)\Sigma\sigma^*_R \quad (2)$$

Similarly, δ(C-β) of VII is related to $\Sigma\sigma^*_R$ as follows:

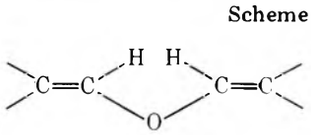
$$\delta(\text{C-}\beta)/\text{ppm} = (99.76 \pm 0.32) + (1.34 \pm 0.14)\Sigma\sigma^*_R \quad (3)$$

In VI and VII the effects of the substituents on the shieldings of the olefinic carbons are based on their polar effects on the stability of the mesomeric structures, electron-releasing substituents favoring the structure with separated charges (see above).

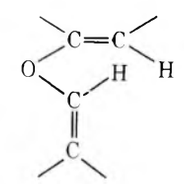
The preceding discussion of the substituent effects deals with divinyl ethers existing[1] mainly in the planar or nearly planar s-trans,s-trans structure shown in Scheme I. If R_3 or R_6 in I is bulkier than a hydrogen atom, this structure becomes less favored because of steric crowding between these groups, and hence the planar or nearly planar s-cis,s-trans rotamer may be the predominating species. A necessary condition for the appearance of this structure is that both R_1 and R_6 (or, alternatively, R_3 and R_4) are not bulkier than H atoms to avoid high steric strain. Of the present compounds, **4–9** and **20–22** are likely to assume the s-cis,s-trans structure. Because of the close analogy in structure between VII and VIII, it might be asked whether the shift δ(C-β) of VIII is linearly related to the polar substituent constant σ^* of the group R, as is the case in VII (eq 3). Table I gives appropriate shift data for R = i-Pr (**4**), R = t-Bu (**5**), and R = Ph (**6**). A fourth member in the series, R = Me, may be obtained by assuming the difference in δ(C-β) between this compound and **5** to be the same (0.48 ppm) as that between **20** and **21**. Thus for R = Me in VIII, δ(C-β) = 95.10 ppm. A least-squares treatment of δ(C-β) against σ_R^* then gives for these compounds:

$$\delta(\text{C-}\beta)/\text{ppm} = (95.09 \pm 0.05) + (1.27 \pm 0.13)\sigma^*_R \quad (4)$$

Scheme I

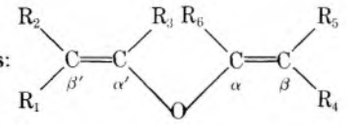


s-trans,s-trans



s-cis,s-trans

Table I. ^{13}C NMR Chemical Shift Data ($CDCl_3$, Internal Me_4Si, δ Values in ppm) for Some Divinyl Ethers:



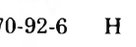
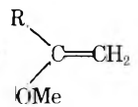
Compd	Registry no.	R_1	R_2	R_3	R_4	R_5	R_6	C-α	C-α'	C-β	C-β'	Other carbons
1	109-93-3	H	H	H	H	H	H	148.84	148.84	93.10	93.10	
2	24268-09-5	Me	H	H	H	H	H	150.09	141.32	90.40	105.58	9.34
3	24268-10-8	H	Me	H	H	H	H	149.93	142.53	91.13	105.99	12.10
4	61463-42-1	H	H	*i*-Pr	H	H	H	147.33	149.28	94.94	84.47	32.81 (CH), 20.47 (Me)
5	66270-88-0	H	H	*t*-Bu	H	H	H	147.82	145.78	94.62	84.39	35.57 (C), 27.94 (Me)
6	66270-89-1	H	H	Ph	H	H	H	147.49	158.76	95.84	88.69	125.40, 128.24, 128.89, 134.98 (aromatic carbons)
7	66270-90-4	H	Me	Et	H	H	H	148.38	156.83	93.32	99.41	11.41 (Me, R_2?), 11.61 (Me), 22.33 (CH_2)
8	66270-91-5	H	Me	*i*-Pr	H	H	H	148.95	156.00	93.08	98.19	11.30 (R_2)
9	66270-92-6	H			H	H	H	149.36	?	93.56	101.68	
10	66270-93-7	Me	H	Et	H	H	H	149.36	154.07	89.34	107.37	10.40 (R_1), 11.61 (Me), 25.83 (CH_2)
11	66270-94-8	Me	H	*i*-Pr	H	H	H	150.42	?	88.77	106.15	10.70 (R_1)
12	66270-95-9	Me	Me	Et	H	H	H	150.01	?	88.69	116.47	17.30 (R_1), 18.44 (R_2), 11.94 (Me), 22.09 (CH_2)
13	66270-96-0	Me	$-(CH_2)_4-$		H	H	H	149.36	157.63	88.69	118.74	15.84 (Me)
14	4696-27-9	Me	H	H	Me	H	H	143.67	143.67	102.82	102.82	9.26
15	61463-31-8	Et	H	H	Me	H	H	143.76	142.46	102.82	110.53	9.26 (R_4), 14.29 (Me), 17.54 (CH_2)
16	61463-35-2	*i*-Pr	H	H	Me	H	H	143.83	141.32	102.90	116.38	9.26 (R_4), 23.15 (Me), 24.20 (CH)
17	4696-29-1	H	Me	H	Me	H	H	142.46	144.89	102.82	104.12	9.26 (R_4), 12.18 (R_2)
18	61463-33-0	H	*i*-Pr	H	Me	H	H	142.86	142.46	103.96	115.89	9.26 (R_4), 23.39 (Me), 27.29 (CH)
19	40716-32-3	Me	Me	H	Me	H	H	143.74	138.38	102.10	112.33	9.33 (R_4), 15.10 (R_1), 19.32 (R_2)
20	66270-76-6	H	H	Me	Me	H	H	140.09	156.65	106.97	85.55	9.33 (R_4), 20.29 (R_3)
21	66270-77-7	H	H	*t*-Bu	Me	H	H	140.58	145.20	106.49	82.06	9.25 (R_4), 28.08 (Me), 35.71 (C)
22	66270-78-8	H	$-(CH_2)_3-$		Me	H	H	141.30	157.05	105.67	97.40	9.33 (R_4), 21.26, 28.89, 31.33 (3 CH_2)
23	66270-79-9	Me	Me	Me	Me	H	H	143.90	?	101.70	114.36	9.09 (R_4), 15.26 (R_3), 16.96 (R_1), 18.91 (R_2)
24	61463-34-1	*i*-Pr	H	H	H	Me	H	144.97	139.86	102.74	117.68	12.18 (R_5), 23.23 (Me), 24.04 (CH)
25	40716-31-2	Me	Me	H	H	Me	H	144.89	136.69	101.77	114.00	12.26 (R_5), 15.03 (R_1), 19.33 (R_2)
26	66270-80-2	Me	Me	Me	H	Me	H	143.90	?	101.05	115.65	12.26 (R_5), 14.69 (R_3)
27	61463-39-6	H	H	*i*-Bu	H	H	Me	156.43	156.26	92.18	94.70	18.84 (R_6), 22.55 (Me), 25.99 (CH), 42.72 (CH_2)
28	66270-81-3	H	H	Ph	H	H	Me	157.40	156.91	92.26	95.84	19.25 (R_6), 125.40, 128.32, 128.65, 135.31
29	66270-82-4	Me	H	Et	H	H	Me	156.46	153.22	84.30	108.83	10.48 (R_1), 11.90 (Me), 20.10 (R_6), 25.22 (CH_2)
30	66270-83-5	H	Me	Et	H	H	Me	157.93	153.83	88.08	107.32	11.65 (R_2), 11.90 (Me), 19.82 (R_6), 20.99 (CH_2)

Table II. ^{13}C NMR Chemical Shift Data for Some Vinyl Ethers:



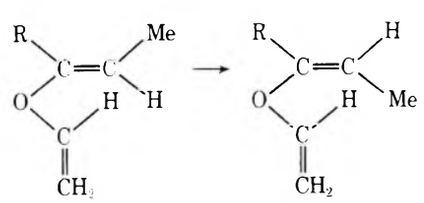
Compd	Registry no.	R	C-α	C-β	MeO	Other carbons
31	107-25-5	H	152.85	85.52	54.74	
32	116-11-0	Me	154.72	80.73	54.66	20.79
33	53119-71-4	*i*-Bu	151.95	81.38	54.58	22.42 (Me), 26.40 (CH), 44.59 (CH_2)
34	4747-13-1	Ph	153.72	81.65	55.11	125.32, 128.08, 128.40, 136.52

The correlation coefficient of the above equation is $r = 0.990$, i.e., a good linear relation between δ(C-β) and σ^*_R is found for VIII. In addition, the sensitivity of δ(C-β) to changes in σ^*_R is almost the same as that in VII. For R = H in VIII, eq 4 gives δ(C-β) = 95.71 ppm, 2.6 ppm higher than the experimental value for **1**. This suggests that in α-substituted divinyl ethers, the extent of conjugation and hence the planarity of the divinyl ether skeleton is slightly reduced relative to the parent divinyl ether molecule **1**.

From the shift data for **20** and **23**, the effects of the two Me groups at C-β' in the latter are obtained as Δ(C-α) = +3.8 and Δ(C-β) = −5.3 ppm, to be compared with the effects of the corresponding Me groups in **19**: Δ(C-α) = +2.4 and Δ(C-β) = −3.5 ppm. The higher effects of the Me groups in **23** point to a change in the conformation of the divinyl ether skeleton on going from **20** to this compound; the planar or nearly planar *s*-cis,*s*-trans structure (in **20**) is not possible for **23** on steric grounds. Since also the *s*-trans,*s*-trans form is out of the question, the molecule is forced to adopt a markedly nonplanar structure in which the O atom conjugates with the propenyl group more effectively than in **20**. At the same time, there is a considerable decrease of conjugation with the other vinyl group, which can be seen from the high α effect (+28.8 ppm) of the two Me groups R_1 and R_2 in **23** on δ(C-β'), while the corresponding α effect is only +21.9 ppm in **19** (in which the Me groups do not necessarily affect the conformation of the divinyl ether skeleton).

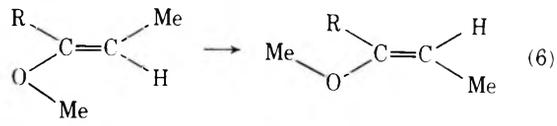
In the case of an α,α'-disubstituted divinyl ether, the molecule cannot be planar and hence a simultaneous unhindered overlapping of the p orbitals on O with both vinyl groups is impossible. Then the O atom may choose to conjugate effectively with just one vinyl group or with both vinyl groups but with reduced efficiency. The latter alternative seems to apply to **27** and **28**. In the former the effect of the Me group on δ(C-β) is −0.9 ppm and that of the *i*-Bu group on δ(C-β') is +1.6 ppm (using **1** as the reference compound), whereas the corresponding effects are −4.8 and −4.1 ppm in **32** and **33**, respectively. Similarly, in **28** the effects of the Me and Ph groups are −0.8 and +2.7 ppm, respectively, to be compared with the corresponding effects in **32** (−4.8 ppm) and **34** (−3.9 ppm). Since the apparent β^π effects in **27** and **28** are essentially more positive than the real β^π effects in the vinyl ethers **32–34**, in which the group (Me, *i*-Bu, or Ph) bound to C-α cannot have any steric influence on the extent of p–π conjugation, it may be concluded that π–p–π conjugation is markedly weaker in **27** and **28** than in **1**, due to the nonplanar nature of these compounds.

It is interesting to consider the changes in δ(C-β) and δ(C-β') in the reaction



(5)

For R = H, Δ(C-β) = −0.7 and Δ(C-β') = −0.4 ppm, i.e., only negligible effects are observed. However, for R = Et Δ(C-β) = −4.0 and Δ(C-β') = +8.0 ppm, and for R = *i*-Pr the corresponding effects are −4.3 and +8.0 ppm, respectively, which means that in these cases the reaction involves enhanced conjugation with the unsubstituted vinyl group but a higher decrease in conjugation with the other vinyl group. It is possible, however, that part of the observed change in δ(C-β') should be ascribed to a decreased through-space shielding effect of the unsubstituted vinyl group on C-β', since in the related reaction 6 Δ(C-β) = +3.6 ppm for R = H, which has been shown to follow not from reduced p–π conjugation (both



(6)

isomers are planar) but rather from a decreased through-space shielding effect of the MeO group on C-β, due to an *s*-cis → *s*-trans conformational rearrangement about the O–(C-α) bond.[3] If R ≠ H in reaction 5, the reaction apparently involves a rotation of the vinyloxy group by ca. 90° about the O–(C-α') bond, which effectively blocks the substituted vinyl group out of conjugation, thus rendering the O atom more capable of donating its lone pair electrons for enhanced conjugation with the other vinyl group. It may be of interest to note that for R = Et or R = *i*-Pr in reaction 6, the values of Δ(C-β) are +13.5 and +14.6 ppm, respectively.[4] The higher shift increments in reaction 6 (for R ≠ H) are understandable, since in the reaction product of each reaction conjugation (with the substituted vinyl group) appears negligible, but in the reagents it should be most pronounced in that of reaction 6, because in the reagent of reaction 5 conjugation is distributed between two vinyl groups.

For the related isomerization reaction **30** → **29**, Δ(C-β) = −3.8 and Δ(C-β') = +1.5 ppm. The *E* → *Z* interconversion of these nonplanar molecules is seen to involve an increase in conjugation with the monoalkyl-substituted vinyl group, whereas the reverse holds for the disubstituted vinyl group. Comparison of δ(C-β') for **29** with that for **10** shows that the additional Me group in the former is capable of decreasing conjugation with the (C-α')=(C-β') double bond, although it should be very small already in **10**.

Finally, it may be mentioned that findings which are well consistent with those observed in the present study have also been recorded for diphenyl ethers; 2,6-dimethyl substitution decreases conjugation of the O atom with the substituted Ph group and increases it with the other Ph group, as shown by the substitution-induced ^{13}C chemical shift changes of +2.9 and −0.9 ppm for the 4 and 4′ carbons, respectively.[5]

Experimental Section

Materials. The preparation and properties of **2–4, 14–19, 24, 25,** and **27** have been described in ref 1 and those of **32, 33,** and **34** in ref 6, 7, and 8, respectively.

Divinyl ether (1) was prepared from di-2-chloroethyl ether by dehydrohalogenation with KOBu-*t*, bp 28 °C (760 Torr).

2-Vinyloxy-3,3-dimethyl-1-butene (5). An equimolar mixture of methyl *tert*-butyl ketone dimethyl acetal and 2-chloroethanol was heated in a distillation apparatus in the presence of a small amount of *p*-toluenesulfonic acid until the evolution of MeOH ceased. The product, 2-(2-chloroethoxy)-3,3-dimethyl-1-butene, was dehydrochlorinated to **5** by heating with an excess of KOH. Pure **5** boiled at 75–78 °C (760 Torr).

α-Vinyloxystyrene (6) was prepared from acetophenone dimethyl acetal and 2-chloroethanol with NH_4Cl as catalyst, followed by dehydrochlorination with KOBu-*t*, bp 31–33 °C (1 Torr).

(*E*)- and (*Z*)-3-Vinyloxy-2-pentene (7 and 10, Respectively). A mixture of **7** and **10** (mainly **7**) was obtained by heating an equimolar mixture of 3-methoxy-2-pentene[7] and 2-chloroethanol in the presence of NH_4Cl until the evolution of MeOH ceased. After dehydrochlorination by KOBu-*t*, the final product was collected at 90–100 °C (760 Torr).

(*E*)- and (*Z*)-3-vinyloxy-4-methyl-2-pentene and 3-vinyloxy-2-methyl-2-pentene (8, 11, and 12, respectively) were prepared from ethyl isopropyl ketone dimethyl acetal and 2-bromoethanol, followed by dehydrobromination with KOBu-*t*, bp 122–125 °C (762 Torr).

1-Vinyloxy-6-methylcyclohexene and 1-vinyloxy-2-methylcyclohexene (9 and 13, respectively) were prepared from the corresponding 1-methoxy derivatives[9] and 2-bromoethanol, followed by treatment with KOBu-*t*, bp 65–70 °C (10 Torr).

2-(*Z*)-Propenyloxypropene (20) was prepared by acid-catalyzed cleavage of acetone di-(*Z*)-propenyl acetal[6] into propionaldehyde and **20**, bp ca. 85 °C (760 Torr).

2-(*Z*)-Propenyloxy-3,3-dimethyl-1-butene (21). Methyl *tert*-

butyl ketone diallyl acetal, bp 90–91 °C (20 Torr), was isomerized to the corresponding di-(*Z*)-propenyl acetal by treatment with KOBu-*t* in Me_2SO, followed by acid-catalyzed cleavage into propionaldehyde and **21**, bp 134 °C (760 Torr).

1-(*Z*)-Propenyloxycyclopentene (22) was prepared by acid-catalyzed cleavage of cyclopentanone di-(*Z*)-propenyl acetal[6] into propionaldehyde and **22**, bp 92–95 °C (105 Torr).

(*Z*)- and (*E*)-2-propenyloxy-3-methyl-2-butene (23 and 26, respectively) were prepared by acid-catalyzed cleavage of methyl isopropyl ketone di-(*Z*)-propenyl acetal [bp 84 °C (20 Torr)]. The products **23** and **26** were separated from the isomeric compounds, (*Z*)- and (*E*)-2-propenyloxy-3-methyl-1-butene, by preparative GLC.

α-Isopropenyloxystyrene (28). See preparation of **6** (1-chloro-2-propanol was used instead of 2-chloroethanol), bp 54–56 °C (2 Torr).

(*Z*)- and (*E*)-3-Isopropenyloxy-2-pentene (29 and 30, Respectively). See preparation of **7** and **10** (1-chloro-2-propanol was used as the alcohol), bp 111–115 °C (760 Torr).

Methyl Vinyl Ether (31). A commercial product was used.

^{1}H NMR Spectra. The spectra were taken at 60 MHz in CCl_4 solution with Me_4Si as internal standard. The shifts are given in δ values (ppm) and the coupling constants in hertz. In many cases, the spectra were recorded on mixtures of isomers, and hence all signals could not always be detected. Thus ^{1}H NMR spectra are not given here for **10, 11,** and **30,** because of their relatively low concentrations in the synthetic mixtures. **1:** 6.36 (H–C_α), 4.17 (H–C_β, J_{cis} = 6.4), 4.48 (H–C_β, J_{trans} = 14.1). **5:** 3.99 and 4.08 ($H_2C_{\beta'}$, J_{gem} = 2.4), 1.09 (3 Me), 6.28 (H–C_α), 4.23 (H–C_β, J_{cis} = 6.0), 4.57 (H–C_β, J_{trans} = 13.4). **6:** 4.36 and 4.76 ($H_2C_{\beta'}$, J_{gem} = 2.6), 7.0–7.6 (aromatic protons), 6.44 (H–C_α), 4.32 (H–C_β, J_{cis} = 6.2), 4.70 (H–C_β, J_{trans} = 13.6). **7:** 4.57 (H–C_β, J_{vic} = 6.8), 1.56 (CH_3–$C_{\beta'}$), 2.14 (CH_2), 1.03 (CH_3), 6.20 (H–C_α), 4.08 (H–C_β, J_{cis} = 6.1), 4.43 (H–C_β, J_{trans} = 14.4). **8:** 4.53 (H–$C_{\beta'}$), 1.60 (CH_3–$C_{\beta'}$), 2.8 (CH), 1.14 (2 Me), 6.23 (H–C_α), 4.13 and 4.51 (H_2C_β). **9:** 4.81 (H–$C_{\beta'}$, J_{vic} = 3.6), 1.06 (CH_3, J_{vic} = 6.9), 1.6–2.2 (ring protons), 6.30 (H–C_α), 4.16 (H–C_β, J_{cis} = 6.1), 4.51 (H–C_β, J_{trans} = 13.7). **12:** 1.55 and 1.64 (2 CH_3–$C_{\beta'}$), 2.18 (CH_2), 0.99 (CH_3), 6.23 (H–C_α), 3.94 (H–C_β, J_{cis} = 6.7), 4.18 (H–C_β, J_{trans} = 13.7). **13:** 1.54 (CH_3), 1.6–2.2 (ring protons), 6.26 (H–C_α), 3.96 (H–C_β, J_{cis} = 6.6), 4.20 (H–C_β, J_{trans} = 14.3). **20:** 3.95 ($H_2C_{\beta'}$), 1.86 (CH_3–$C_{\alpha'}$), 6.11 (H–C_α), 4.67 (H–C_β, J_{cis} = J_{vic} = 6.7), 1.59 (CH_3–C_β). **21:** 3.93 and 4.02 ($H_2C_{\beta'}$, J_{gem} = 2.4), 1.13 (3 Me), 6.09 (H–C_α), 4.68 (H–C_β, J_{cis} = 6.4, J_{vic} = 7.0), 1.60 (CH_3–C_β). **22:** 4.55 (H–$C_{\beta'}$), 1.8–2.5 (ring protons), 6.20 (H–C_α), 4.60 (H–C_β, J_{cis} = 6.4, J_{vic} = 6.9), 1.59 (CH_3–C_β). **23:** 1.6 (2 CH_3–$C_{\beta'}$), 1.75 (CH_3–$C_{\alpha'}$), 5.87 (H–C_α), 4.37 (H–C_β, J_{cis} = 6.0, J_{vic} = 6.8), 1.6 (CH_3–C_β). **26:** 1.6 (2 CH_3–$C_{\beta'}$), 1.75 (CH_3–$C_{\alpha'}$), 6.03 (H–C_α), 4.70 (H–C_β), 1.6 (CH_3–C_β). **28:** 4.67 and 5.04 ($H_2C_{\beta'}$, J_{gem} = 1.6), 7.1–7.6 (aromatic protons), 4.20 and 4.13 (H_2C_β), 1.91 (CH_3–C_β). **29:** 4.80 (H–$C_{\beta'}$, J_{vic} = 6.9), 1.57 (CH_3–$C_{\beta'}$), 2.21 (CH_2), 0.97 (CH_3, J_{vic} = 6.9), 1.79 (CH_3–C_α), 3.77 and 3.91 (H_2C_β).

^{13}C NMR Spectra. The spectra were taken at 15.03 MHz with $CDCl_3$ as solvent and Me_4Si as internal standard. Total sample concentration was 20% (v/v). Since many of the spectra were taken on mixtures of isomers, there remained some uncertainty in signal assignment, and thus shift data are not given for all the carbons of the compounds studied. However, the signals of the most important carbon atoms (C-β and C-β′) could be assigned with certainty in all cases.

Acknowledgment. The author is grateful to Miss Leena Tuominen, B.S., for some synthetic aid.

Registry No.—Di-2-chloroethyl ether, 111-44-4; methyl *tert*-butyl ketone dimethyl acetal, 62038-48-6; 2-chloroethanol, 107-07-3; 2-(2-chloroethoxy)-3,3-dimethyl-1-butene, 66270-84-6; acetophenone dimethyl acetal, 4316-35-2; 3-methoxy-2-pentene, 41623-41-0; ethyl isopropyl ketone dimethyl acetal, 51945-95-0; 2-bromoethanol, 540-51-2; 1-methoxy-6-methylcyclohexene, 1728-37-6; 1-methoxy-2-methycyclohexene, 1728-38-7; acetone di-(*Z*)-propenyl acetal, 62322-38-7; methyl *tert*-butyl ketone dialkyl acetal, 66270-85-7; methyl *tert*-butyl ketone di-(*Z*)-propenyl acetal, 66270-86-8; cyclopentanone di-(*Z*)-propenyl acetal, 62322-37-6; methyl isopropyl ketone di(*Z*)-propenyl acetal, 66270-87-9; 1-chloro-2-propanol, 127-00-4.

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MINDO/3 Calculations on the Stability of Criegee Carbonyl Oxides

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Calculations using MINDO/3 are presented which support the Bailey modification of the Criegee mechanism for ozonolysis. An activation enthalpy for syn–anti interconversion of the planar carbonyl oxides of formaldehyde and acetaldehyde of 25.3 and 24.5 kcal/mol, respectively, is calculated. The cyclization of formaldehyde carbonyl oxide to 1,2-dioxocyclopropane is shown (according to MINDO/3) to proceed with an activation enthalpy of 27.2 kcal/mol. The carbonyl oxide is calculated to be thermodynamically capable of acting as an epoxidizing agent and of giving molecular oxygen on reacting with itself.

The proposal by Criegee[1] of a general mechanism for the reaction of ozone with alkenes involving as an intermediate a carbonyl oxide ($R_1R_2C^+$–O–O^-) has been highly successful in accounting for a considerable body of experimental facts.[2] The remaining questions center around the apparent stereoselectivity in the cis/trans ratio of the secondary ozonide (1,2,4-trioxolane) products.[3] The suggestion that the stereospecificity arises from the preferential formation of syn or anti carbonyl oxides, which then display different reactivities, is partly based on the premise of nonequilibration of the syn and anti carbonyl oxides.[4,5] This presumed nonequilibration is in turn based on the configurational stability of the syn and anti oximes.[6] If equilibration of syn and anti carbonyl oxides were rapid compared with reaction to form secondary ozonides then there should be no such stereoselectivity in the 1,2,4-trioxolanes.

There have been several semiempirical molecular orbital studies of the primary ozonide (1,2,3-trioxolane) and its breakdown[7-9] and two ab initio calculations on the methylene peroxide (CH_2O_2) system.[10,11] The former studies never address the configurational stability of the carbonyl oxide and the latter studies partially assume a geometry (bond lengths) and therefore do not optimize all geometric parameters and in addition deal only with the static species rather than the

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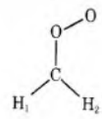
Table I. Formaldehyde Carbonyl Oxide



	$\Delta H°_f$, kcal/mol	Bond length, Å (C–H, C–O, O–O)	Bond angle, deg (H_1CO, H_2CO, COO)	Dipole moment, D	Ionization potential, eV
This work[a]	+15.8	1.110, 1.252, 1.268	116.1, 129.5, 125.7	3.54	9.67
Ref 10[b]		1.09, 1.44, 1.48	116, 116, 115	6.08	
Ref 11[c]	48	1.08, 1.35, 1.37	120, 120, 103	3.03	

[a] Bond lengths and angles were optimized. [b] Bond lengths were assumed and bond angles were optimized. [c] All geometry parameters were assumed.

Table II. 1,2-Dioxocyclopropane

	$\Delta H°_f$, kcal/mol	Bond length, Å (C–H, C–O, O–O)	Bond angles, deg (HCO, COO)	Dipole moment, D	Ionization potential, eV
This work	−17.9	1.123, 1.342, 1.456	126.3, 47.17	2.15	11.14
Ref 10[a]		1.09, 1.44, 1.48	−, 60	3.15	
Ref 11[b]	7.5[c,d]	1.08, 1.436, 1.45	115.6, 59.7		

[a] Bond lengths and angles were optimized. [b] Bond lengths were assumed and bond angles were optimized. [c] All geometry parameters were assumed. [d] Estimated from thermochemical data.

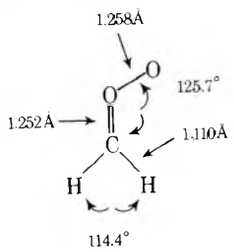
interconversion among the various isomers.

This work uses MINDO/3, a version of the MINDO semiempirical SCF–MO treatment, developed and extensively tested by Dewar and co-workers to explore the configurational stability of the carbonyl oxide.[12,13] MINDO/3 has been used by Dewar and co-workers with reasonable success for calculations on ozone, oxygen, and cyclic peroxides,[12,14] and it seemed reasonable to expect similar success on the carbonyl oxide system. Also the explicit inclusion of electron and nuclear repulsion make the method particularly suitable where there are adjacent heteroatoms with lone pair repulsions and electronegativity effects giving rise to polar bonds.[9]

Results and Discussion

Criegee Formaldehyde Carbonyl Oxide. The calculated properties of the simplest of the Criegee carbonyl oxides, formaldehyde carbonyl oxide, are listed in Table I. For comparison the results of previous calculations are also listed. It was necessary in this work to include configuration interaction (mixing of the lowest doubly excited configuration) since the energy lowering on mixing was significant (22.8 kcal/mol without CI, 15.8 with).[15]

The geometry for the formaldehyde carbonyl oxide, **1**, as shown below was planar (±0.1°) with significant increases in energy on out-of-plane hydrogen movement. The O–O bond



1

length found is more like ozone (1.278 Å)[16] than that of simple peroxide models (approximately 1.4 Å) as might be expected considering the orbital similarity of ozone and the formaldehyde carbonyl oxide. The C–O bond length is between that of a formal double bond (1.23 Å) and that of a formal single bond (1.43 Å) again reflecting the allyl aspect of the bonding. The relatively high dipole moment reflects the electron density decrease on carbon and increase on oxygen. All of the above is reasonably consistent with the commonly written structure for the carbonyl oxide as a hybrid of two charge separated structures as shown below.

$$CH_2 = O^+—O^- \leftrightarrow C^+H_2—O--O^-$$

With the large dipole moment, solvation energy may be important in stabilizing this species relative to other methylene peroxide isomers. Trapping experiments in polar solvents (hydrogen bonding solvents like acetic acid or alcohols) may lead to selecting the chemistry of the carbonyl oxide. Further, the necessary inclusion of configuration interaction in the calculation of the ground state properties of the carbonyl oxide would indicate some singlet "biradicaloid" character.[15] The "biradicaloid" character of the species would also be subject to solvent effects, diminishing in the more polar solvent. Hence solvent effects could be of two sorts: (a) on the stability of the carbonyl oxide and (b) on the reactivity (radical or ionic) of the carbonyl oxide. In the absence of solvents, radical reactivity *may* predominate giving rise to a different manifold of reactions even though the planar Criegee carbonyl oxide is the principal intermediate. Experiments in the gas phase are most consistent with radical reactivity.[17]

1,2-Dioxocyclopropane. The cyclic 1,2-dioxocyclopropane is calculated to be more stable than the planar carbonyl oxide, **1**. The results in this regard are consistent with those of other calculations (see Table II). However, the very negative $\Delta H°_f$ of −17.9 kcal is probably too low. MINDO/3 is known to overestimate the stability of ethylene oxide by 13.9 kcal/mol and could be expected in this three-membered oxygen heterocycle to also overestimate stabilities by a like amount.[18,19] Applying the 13.9 kcal as a correction factor would make the $\Delta H°_f$ = −4.0 kcal which is not far different than an estimate based on Benson's group additivity method of +0.9 kcal/mol (see Table III).[20] The Benson method assumes a value of +27.6 kcal for a ring strain correction which may be low in this case.

The polarity of species **2** as measured by its dipole moment indicates that it is less polar than the species **1** and hence would be less sensitive to solvent polarity than species **1**.

The methylene peroxide system differs from the O_3 system

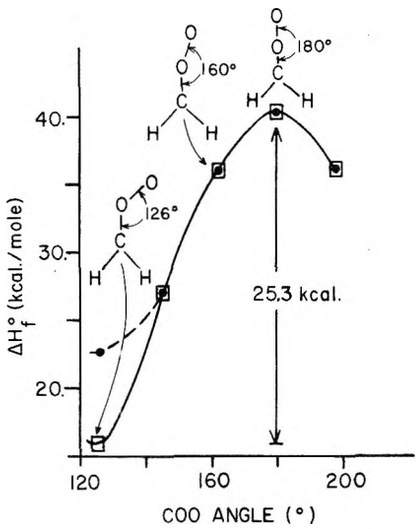


Figure 1. COO angle variation for formaldehyde carbonyl oxide; energy and geometry of the resulting species: (●) without CI, (□) with CI.

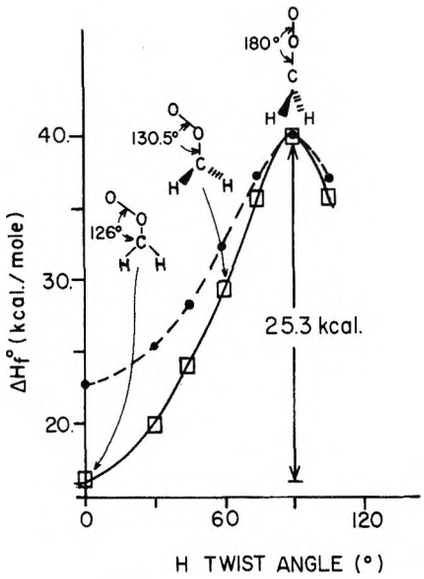


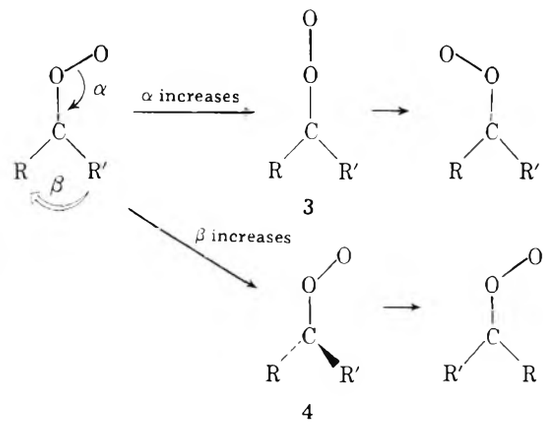
Figure 2. Hydrogen twist angle variation for formaldehyde carbonyl oxide; energy and geometry of the resulting species: (●) without CI, (□) with CI.

Table III. Group Addivity Estimate of $\Delta H°_f$ for 1,2-Dioxocyclopropane

	$\Delta H°_f$, kcal/mol
C-(O)$_2$(H)$_2$	−17.7
2(O-(O)(C))	−9.0
Ring strain correction	+27.6
$\Delta H°_f$	0.9

in that the cyclic form is more stable than the open or bent form. This is undoubtedly due, as suggested by Goddard and co-workers, primarily to strength of the C–O σ bond vis a vis the O–O σ bond.[11]

Syn–Anti Isomerization. The configurational integrity of the syn and anti carbonyl oxides can be lost by rapid formation (relative to reaction to give secondary ozonides) of a species in which a plane exists including the COO group that is perpendicular to the plane defined by the RCR′ group. This is most easily envisioned as proceeding by either an increase in the COO angle, α, or by an internal rotation of the terminal carbon about the C–O bond, an increase in the angle β; the two limiting cases are shown below.[21] In the first case the pseudo-linear species, **3**, is the required symmetrical species. In the second case the species, **4**, a perpendicular form of the carbonyl oxide, is the symmetrical intermediate.

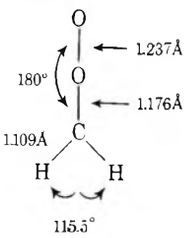


3 4

If species 1 is used as a substrate for the above described geometric distortions the reaction is of course a degenerate one, that is, the product is identical with the reactant. The reaction can, however, serve as a simple model for loss of syn–anti integrity.

In the first case where the COO angle is the reaction coordinate calculations were carried out at several points along the reaction path with optimization of all other bond lengths, bond angles, and twist angles. The H's on the carbon were "free" to twist out of the plane. The results of the calculations are plotted in Figure 1.

Shown are calculations with and without CI. Clearly as the reaction proceeds the biradical character of the species decreases as the transition state is approached. The point of maximum enthalpy of formation along the reaction is the species corresponding to **3** with the COO bond angle at 180°. The C–O bond decreases uniformly reaching 1.176 Å in the linear species. The O–O bond length increases marginally to 1.273 Å. Each of the species along the reaction coordinate is essentially planar with the H's no more than 0.2° out of the plane. The geometry of the species is given below:



The results of the calculations for the syn–anti isomerization via twisting of the CH_2 group about the CO bond axis are shown in Figure 2. Here all other geometric parameters were optimized. There was little difference between a coordinated twist of the CH_2 group about the CO axis and simply twisting a single hydrogen and allowing optimization of the other hydrogen's position. The results for the (single H) twist are shown. Again shown are calculations with and without CI.

As can be seen in the species drawn in Figure 2 the COO angle increases as the twist progresses, reaching the same transition state as in the previous case of forcing the COO angle open. The energy gradient along a path increasing the COO angle is clearly less steep than that decreasing the COO angle otherwise the species on twisting could close to the dioxocyclopropane (vida infra).

The enthalpy increase to reach the transition state species is 25.3 kcal/mol. With the assumption of the collision factor

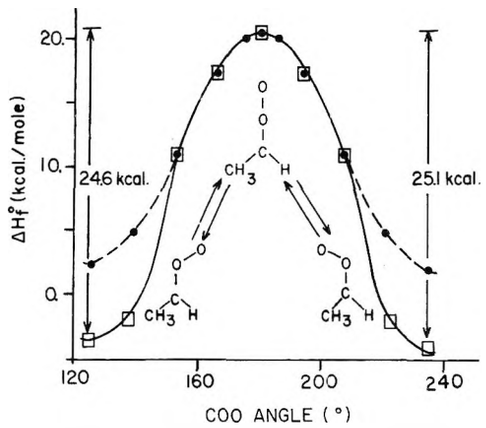
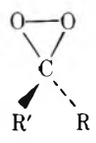


Figure 3. COO angle variation for anti–syn conversion of acetaldehyde carbonyl oxide; energy of the resulting species: (●) without CI, (□) with CI.

(A) in the Arrhenius equation of about 5×10^{12} (typical for cis–trans isomerizations) one calculates a first-order rate constant for syn–anti isomerization at 0 °C of 3×10^{-8} s^{-1}.[22] Such a rate constant for the syn–anti isomerization is far too slow to compete with other fates for as reactive a species as the carbonyl oxide. Methodological errors in the calculation of the relative energies of the various species may however give rise to a very large difference between the actual and calculated rate constants.

In Figure 3 is shown the results of calculations on the anti–syn transformation for the planar acetaldehyde carbonyl oxide. The process is forced to occur by expansion of the COO bond angle. The transition state is again a pseudo-linear species with a $\Delta H^{\ddagger}$ of 24.6 kcal. The reverse reaction does not differ significantly in rate since the syn form is only 0.5 kcal more stable than the anti. There is therefore little variation in $\Delta H^{\ddagger}$ with simple alkyl substitution. It would not seem unreasonable to suggest that the syn–anti isomerization reaction is not competitive with other reactions.

Cyclization of the Planar Carbonyl Oxide. The permanancy, however, of chemically distinguishable initially formed carbonyl oxides depends not only on how rapidly the syn and anti forms interconvert but also on whether some other species intervenes which equates the carbon substituents. The substituted 1,2-dioxocyclopropane, **4**, is such a



4

species. Subsequent reactions of **4** will not account for the dependency of secondary ozonide composition on the cis/trans nature of the starting alkene. It is therefore of some interest to explore the question of how rapidly such a species is likely to form from a planar Criegee carbonyl oxide.

Since 1,2-dioxocyclopropane is also more stable thermodynamically than the Criegee formaldehyde carbonyl oxide it is clearly a possibility that the dioxocyclopropane is a likely fate of all planar carbonyl oxides and as such may well account for some portion of the chemistry observed in ozonolysis reactions.

The rate of the transformation shown below then becomes an important question. Such a process can be accomplished by simultaneously (although not necessarily synchronously) reducing the COO bond angle and twisting the hydrogens out of the plane of the COO group. It is necessary to use both degrees of freedom to cause cyclization since as already mentioned a simple CH_2 twisting opens up the COO angle. A compression of the COO angle will cause the cyclization but the CH_2 group does not twist until late in the reaction and gives a somewhat high $\Delta H^{\ddagger}$. A smoother transition occurs with a forced synchronous motion coupling CH_2 out-of-plane rotation to COO bond angle compression with optimization of all other geometric parameters. The transition state enthalpy proved relatively insensitive to the CH_2 twist angle, so that the $\Delta H^{\ddagger}$ derived by the synchronous motion for ring closure should be close to the minimum $\Delta H^{\ddagger}$. The left-hand portion of Figure 4 shows the results of the calculations on the cyclization reaction. The transition state occurs at a COO bond angle of about 91° and $\Delta H°_f$ of 42.9 kcal. This gives $\Delta H^{\ddagger}$ of 27.2 kcal/mol for the formation of 1,2-dioxocyclopropane from the planar Criegee carbonyl oxide. This value for the $\Delta H^{\ddagger}$ may be low since, as mentioned, MINDO/3 underestimates strain. The 27.2 kcal/mol may therefore be regarded as a minimum estimate for $\Delta H^{\ddagger}$.

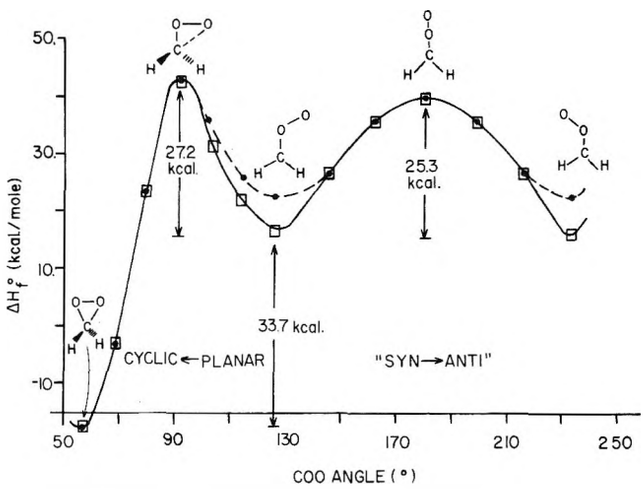
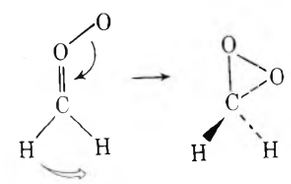
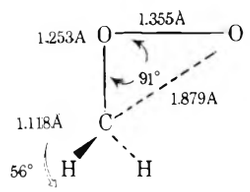


Figure 4. $\Delta H°_f$ vs. COO angle for formaldehyde carbonyl oxide "syn–anti" conversion and closure to 1,2-dioxocyclopropane: (●) without CI, (□) with CI.





Such a large activation enthalpy is inconsistent with the notion of the cyclic species being important in the solution phase. In the gas phase where collisional deactivation is slower than in solution a vibrationally hot planar carbonyl oxide may more readily be transformed into the cyclic form.[17]

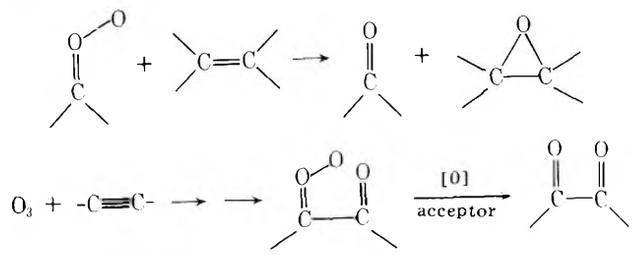
Figure 4 also summarizes the transformations discussed for the planar formaldehyde carbonyl oxide. With the barriers to configuration loss as indicated the simple planar carbonyl oxides, once formed in a particular configuration, are likely to remain in that configuration till they react to form more stable products. The syn–anti isomerization or the cyclization of the carbonyl oxide may be of some importance in the chemistry of the more hindered carbonyl oxides (like that for acetone) which do not give secondary ozonides.[2]

Table IV. MINDO/3 Calculations of $\Delta H°_f$ For Criegee Carbonyl Oxides

Molecule	Registry no.	$\Delta H°_f$, kcal/mol
		+15.8
	65339-04-0	−3.8
	65339-03-9	−4.3
	65339-02-8	−17.3

Thermochemical Calculations. It has been suggested by Fliszar and Renard that the cleavage of the initial five-membered ozone addition product is influenced by the relative stabilities of the two fragments, the carbocation stabilizing ability of the substituents being important.[23] Utilizing the results of the calculations on variously substituted Criegee carbonyl oxides (summarized in Table IV) the thermochemical data shown in Table V were compiled for that initial cleavage reaction as well as several other types of reactions possible for the carbonyl oxide. The thermochemical data for species other than the carbonyl oxide were taken from standard sources.[24] Thermodynamically the favored cleavage pathway is to yield the more highly alkyl substituted carbonyl oxide, in line with results of Fliszar and Renard.

The Criegee carbonyl oxide is potentially an oxygen atom transfer reagent. It has been suggested by Keay and Hamilton that a cyclic form of the carbonyl oxide generated in the ozonolysis of acetylenes at low temperature is responsible for the epoxidation of subsequently added alkenes.[25] Also the observation of epoxides as by-products in the ozonolysis reaction of alkenes and α-diketones as by-products in the ozonolysis of alkynes may be due to the oxygen atom transfer ability of the carbonyl oxide.[2,26] The type of reaction envisioned is illustrated below. The results indicate the reactions are possible thermodynamically proceeding with large negative enthalpies.



The cyclic species is somewhat less exothermic as an epoxidizing agent due to its greater stability. As one would expect the exothermicity for epoxidation clearly decreases as the stability of the carbonyl oxide increases.

Carbonyl oxides have also proved to be elusive species, none having ever been unambigously identified spectroscopically. They are transient species which may display unexpected reactivities. If the species does indeed possess considerable diradical character as suggested by the calculations, the reaction illustrated below may be possible in analogy with the corresponding reaction of peroxy radicals.[27]

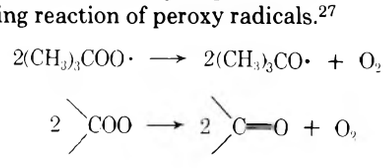
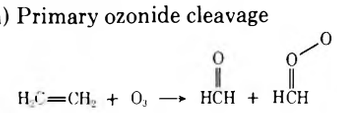
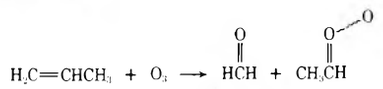
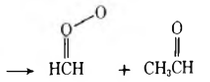
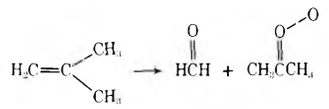
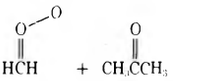
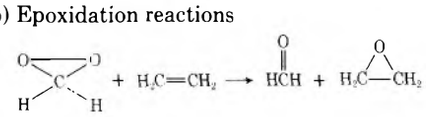
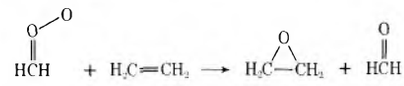
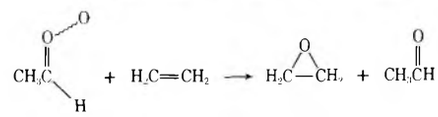
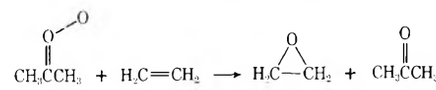
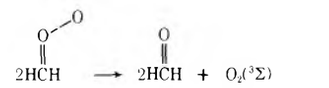
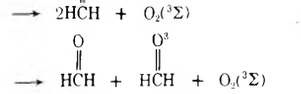
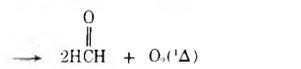
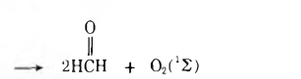
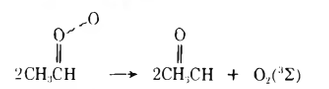
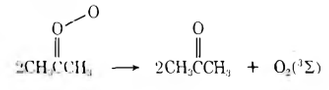


Table V. Thermochemical Calculations

	$\Delta H°$, kcal/mol
(a) Primary ozonide cleavage	
	−61
	−69
	−66
	−78
	−72
(b) Epoxidation reactions	
	−52
	−67
	−61
	−52
(c) O_2 production	
	−83
	−11[b]
	−61
	−45
	−72
	−69

[a] $\Delta H°_f$ as estimated in Table I was used. [b] Formaldehyde triplet at 72 kcal above ground state: G. W. Robinson, *Can. J. Phys.*, **26**, 1761 (1957). [c] Registry no. 74-85-1. [d] Registry no. 115-07-1. [e] Registry no. 115-11-7.

The thermochemical data support the feasibility of O_2 production from two carbonyl oxides and even allow for the production of excited state products.

Conclusion

Calculations using MINDO/3 support the Bailey modification of the Criegee mechanism for ozonolysis in which the

carbonyl oxide is proposed to exist in syn or anti forms. The barriers to syn–anti interconversion and to cyclization of the carbonyl oxide are shown to be substantial so that the chemistry observed in the ozonolysis reaction in solution is very likely that of the initial mixture of carbonyl oxides generated by cleavage of the primary ozonide. The 1,2-dioxocyclopropane is shown, however, to be more stable than the carbonyl oxide, in agreement with previous studies.

Thermochemical calculations are permissive for various fates of the carbonyl oxide including reduction via epoxidation and oxygen formation.

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Registry No.—Formaldehyde carbonyl oxide, 62024-18-4; 1,2-dioxocyclopropane, 157-26-6.

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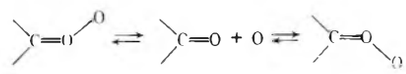
(21) Another route for syn–anti interconversion is via the carbonyl oxide dissociation and recombination as indicated below. The intermediacy, however, of an oxygen atom seems unlikely in the solution phase reactions.[2]



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1,2-Diazetidine Conformation. Double Nitrogen Inversion[1,2]

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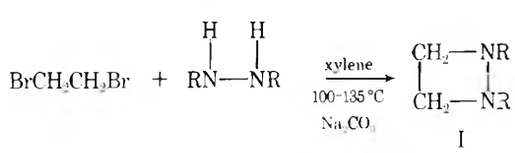
Several 1,2-dialkyl-1,2-diazetidines have been synthesized and their NMR spectra examined as a function of temperature. The methylene protons exhibited an AA'BB' pattern at temperatures below 0 °C, but as the temperature was raised, the AA'BB' pattern broadened and then coalesced into a singlet. Line-shape analysis as a function of temperature gave ΔH^* values in the range 14.9–18.9 kcal mol^{-1} and ΔS^* values in the range +1 to −7 cal deg^{-1} mol^{-1}. The effect of *N*-alkyl substituents on the rate of double nitrogen inversion and on the 1,2-diazetidine ring conformation is discussed. Mass spectral data of 1,2-diazetidines are presented.

Conformational studies on saturated ring systems containing two adjacent nitrogen atoms have been the subject of a number of reports during the last several years.[3-19] However, there appears to have been only a few reports on the 1,2-diazetidine ring system.[8,16-19] We would like to report the synthesis of several 1,2-dialkyl-1,2-diazetidines and the results of a proton magnetic resonance study on these interesting compounds.

The 1,2-dialkyl-1,2-diazetidines used in this study were prepared by direct reaction of 1,2-dibromoethane and the corresponding 1,2-dialkylhydrazine in hot xylene in the presence of anhydrous sodium carbonate.

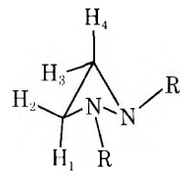


I

This procedure was reported by Horwitz[20] in a patent. However, we were not able to prepare 1,2-dimethyl-1,2-diazetidine in a useful yield using the procedure in the patent. It was found that the yields could be increased substantially by using a large excess of ethylene bromide (a considerable amount is lost during the reaction by undergoing elimination) and adding it dropwise to the 1,2-dialkylhydrazine and sodium carbonate in a large volume of xylene over a period of several hours. This high dilution technique gave yields as follows (R's, yield): CH_3, 32%; C_2H_5, 28%; $(CH_3)_2CH$, 60%; $(CH_3)_3C$, 2.3%.

The 1,2-dimethyl-1,2-diazetidine prepared by the above method was contaminated by an impurity (ca. 10%) which could not be removed, but it did not interfere with the NMR study. The 1,2-di-*tert*-butyl-1,2-diazetidine was prepared only once in 2.3% yield. In spite of several attempts, we were never able to isolate it a second time. Other dibromides can be used. Reaction of 1,2-dibromopropane with 1,2-diethylhydrazine

Table I. 60 MHz NMR Parameters of the Methylene Hydrogens in 1,2-Dialkyl-1,2-diazetidines



Compd	Registry no.	Substituents R's	Chemical shift, Hz		Coupling constants, Hz			
			$H_1 = H_4$	$H_2 = H_3$	J_{14}	$J_{12} = J_{34}$	$J_{13} = J_{24}$	J_{23}
I	52433-27-9	CH_3[b]	173.41	207.16	10.14	−6.27	7.90	2.76
II	66303-57-9	CH_3CH_2[c]	178.24	208.42	9.85	−6.50	8.54	3.17
III	66303-58-0	$(CH_3)_2CH$[d]	180.23	201.14	8.79	−7.24	9.26	4.57
IV	66303-59-1	$(CH_3)_3C$[e]	192.70	222.80	9.80	−9.04	9.10	4.61
V	66303-60-4	1,2-Diisopropyl-3-phenyl-1,2-diazetidine[a,f]						
		$H_1 = 175$, $H_2 = 225$, $H_4 = 254$			$J_{12} = -6.7$, $J_{14} = 8.6$, $J_{24} = 8.6$			

[a] Same numbering as above with phenyl in place of H_3. [b] CH_3, 2.36 ppm. [c] CH_3, 0.87 ppm; CH_2, 2.55 ppm. [d] CH_3, 0.91 ppm; CH, 2.82 ppm. [e] CH_3, 0.83 ppm. [f] CH_3, 0.95 ppm; CH of isopropyl groups, 2.90 ppm.

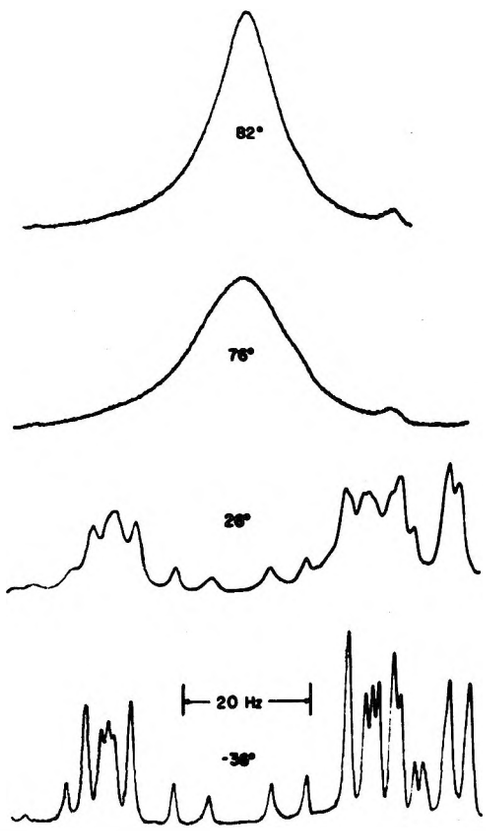


Figure 1. NMR spectra of 1,2-diethyl-1,2-diazetidine. The right side of the spectrum shows part of the ethyl CH_2 quartet and the peak due to $CHCl_3$.

gave a 24% yield of the 1,2-diethyl-3-methyl-1,2-diazetidine. However, GLC indicated that it was contaminated with an impurity and it was not investigated further. Reaction of 1-phenyl-1,2-dibromoethane with 1,2-diisopropylhydrazine gave only a 2% yield of the 1,2-diazetidine.

The 1,2-dialkyl-1,2-diazetidines are very stable compounds. For example, 1,2-di-*tert*-butyl-1,2-diazetidine survived distillation at 155 °C. 1,2-Diethyl-1,2-diazetidine was recovered after treatment with sodium amide at room temperature for 2 weeks. Butyllithium had no effect on 1,2-diisopropyl-1,2-diazetidine, nor did concentrated hydrochloric or 98% sulfuric acid at room temperature. Catalytic hydrogenation (50 psi) of 1,2-diisopropyl-1,2-diazetidine over platinum on charcoal failed to cleave the N–N bond.

The NMR spectra of the 1,2-dialkyl-1,2-diazetidines showed the methylene hydrogens as a well-defined AA'BB' pattern at temperatures below 0 °C. A typical set of spectra are given in Figure 1. Using the LAOCN3 computer program,[18] the chemical shifts and coupling constants were assigned as given in Table I.

Examination of the coupling constants in Table I reveals a very large difference in J_{14} and J_{23}. This large difference indicates clearly that the 1,2-diazetidine must be highly puckered.

We have assigned the larger of the coupling constants, $J_{1,4}$, to the diaxial hydrogens and the smaller of the two to the equatorial hydrogens in line with the anticipated effect of a larger dihedral angle for the diaxial hydrogens. Using a modified Karplus relationship[19] we estimated the dihedral angle between H_1 and H_4 to be 166, 161, 152, and 159° for the dimethyl, diethyl, diisopropyl, and di-*tert*-butyl groups, respectively. Although such calculations are not very reliable, the difference between J_{14} and J_{23} (10.14 and 2.76) for the 1,2-dimethyl-1,2-diazetidine is so large that it is difficult to rationalize the data without assuming a dihedral angle of this magnitude. Rademacher[16] estimated the dihedral angle between the nonbonded electron pairs on nitrogen in 1,2-dimethyl-1,2-diazetidine as 145°. This is difficult to compare with our data without making assumptions as to the bond angles around the nitrogen, but the numbers are at least of the right order of magnitude.

As one increases the bulk of the groups from methyl to ethyl to isopropyl a regular increase in J_{23} and a decrease in J_{14} is noted, suggesting that the ring is flattening out somewhat. A similar result has been observed in 1-alkylazetidines,[23] where variation of the alkyl group from methyl to ethyl to isopropyl to *tert*-butyl causes flattening of the ring.

Examination of the coupling constants and chemical shifts for 1,2-di-*tert*-butyl-1,2-diazetidine suggest that it may have a somewhat different conformation. For example, when the substituent increases in size from methyl to isopropyl, there is a regular decrease in J_{14} but as you go to the *tert*-butyl group, J_{14} increases again. There is also a significant downfield shift of both H_1 and H_4 in the di-*tert*-butyl compound. If one builds models of the di-*tert*-butyl compound and assumes a

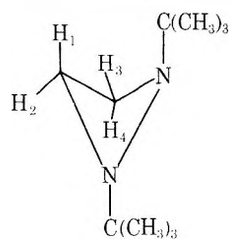


Table II. Rate Constants for Nitrogen Double Inversion in 1,2-Diazetidines

1,2-Dimethyl		1,2-Diethyl		1,2-Diisopropyl		1,2-Di-*tert*-butyl	
T, °C	k, s^{-1}	T, °C	k, s^{-1}	T, °C	k, s^{-1}	T, °C	k, s^{-1}
18.0	5.0	26	6.0	22	2.2	120	8.0
25.5	8.0	29	8.0	25	3.0	143	30
37.0	20.0	34	12.0	29	4.0	148	40
43.0	38.0	40	20.0	35	8.5	155	66
46.0	50.0	47	45.0	38	11		
55.0	74.0	54	70.0	44	22		
53.0	86.0	59	100	48	30		
57.0	121	63	130	49	35		
59.5	143	66	154	53	40		
67.0	196	71	220	56	50		
72.0	300	75	312	66	100		
		79	380				
		82	500				
		85	600				

Table III. Activation Parameters for Nitrogen Inversion in 1,2-Diazetidines

Compd	R's	ΔH^*, kcal mol^{-1}	ΔS^*, cal deg^{-1} mol^{-1}
I	CH_3	14.9 ± 0.8	−4.4 ± 2.4
II	C_2H_5	15.9 ± 0.5	−1.9 ± 1.5
III	$(CH_3)_2CH$	17.1 ± 1.0	+1.1 ± 3.0
IV	$(CH_3)_3C$	18.9 ± 1.2	−6.9 ± 2.8

dihedral angle of 150–160°, one comes to the conclusion that the more stable conformation in this case is probably the one with the *tert*-butyl groups diaxial.

The effect of the di-*tert*-butyl groups is noted in the coalescence temperature of the methylene hydrogens; whereas the coalescence temperatures of the dimethyl, diethyl, and diisopropyl compounds are in the 60–70 °C range (Figure 1), the coalescence temperature of the di-*tert*-butyl compound is about 155°. The di-*tert*-butyl compound still exhibits a sharp AA'BB' spectrum even at a temperature of 72 °C.

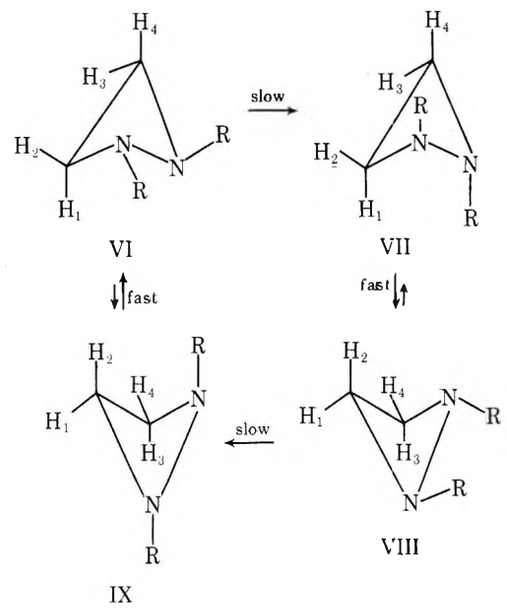
In order to obtain more quantitative information, the changes in the NMR spectra of compounds I–IV were studied as a function of temperature and the rate of nitrogen inversion was determined by comparison of the line shapes of the experimental spectra with those calculated using the DNMR program.[24] The rate constants obtained are listed in Table II.

Examination of the data in Table II reveals that the relative rates of nitrogen inversion at 66° are 1:0.78:0.51:0.74 × 10^{-3}. The results indicate only small differences in rates of inversion in the dimethyl, diethyl, and diisopropyl compounds but a very restricted inversion in the di-*tert*-butyl compound. These results contrast with those on 1-alkylaziridines, where steric acceleration has been reported.[25,26] The activation parameters, ΔH^* and ΔS^*, are listed in Table III.

The enthalpy of activation increases systematically with increasing size of the alkyl group. In the dimethyl, diethyl, and diisopropyl cases the increasing enthalpy of activation is offset by an increasing entropy of activation so that the total rate and ΔG^* is not affected greatly. In the di-*tert*-butyl case the entropy swings back negative, suggesting a high degree of steric crowding in the transition state.

The free energy of activation for 1,2-dimethyl-1,2-diazetidine (16.4 kcal/mol) is much larger than that reported by Ogden[8] for the perfluoro derivative (7.25 kcal/mol). The free energy is also much larger than that reported by Anderson[7] for 1,2-dimethylpyridazine (11.7 kcal/mol) or by Junge and Staab[6] for the corresponding benzopyridazine (12.0 kcal/mol). Mannschreck and co-workers[4] examined the NMR spectra of some 1,2-dialkyldiaziridines and found that the rate of nitrogen inversion was slow. They calculated the barrier to inversion in 1-isopropyl-3,3-dimethyl-1,2-diaziridine to be 23 kcal/mol, a value higher than those in Table III. Fahr and co-workers examined 1,2-diaryl-1,2-diazetidinones and reported ΔG^* values of 13–16 kcal/mol based on coalescence temperatures.[19] Philips reported an E_a of 8.0 kcal/mol for 1,2-dicarboethoxy-3,3,4,4-tetrafluoro-1,2-diazetidine apparently based on coalescence temperature.[17] However, these data are in doubt because Carlson, Schapp, and Raban have shown that the kinetic process observed for 1,1-dicarboethoxy-3,3,4,4-tetramethoxy-1,2-diazetidine is due to restricted rotation of the carboethoxy groups around the C–N bond, a process which has a ΔG^* of 13.6 kcal/mol.[18]

The NMR data presented can best be rationalized by the following conformational changes:



If the inversion at nitrogen is slow compared to ring inversion, the rate of the exchange process (VI to VIII) would be controlled by the rate of inversion at nitrogen (VI to VII or VIII to IX). At low temperature the AA'BB' spectrum observed would be that of VI (or VIII), since the concentration of VII (or IX) would be expected to be low for the dimethyl, diethyl, and diisopropyl cases due to 1,3 interactions. Apparently what little steric interaction there is between the alkyl groups on the adjacent nitrogens leads only to flattening of the ring with little effect on nitrogen inversion. In the di-*tert*-butyl case, the rates may be reversed with VII and IX being the more stable structures and the rate-determining step in the ex-

change process would then be conversion of VII to VI (or IX to VIII).

In this rationalization, the possibility of an axial-equatorial isomer has been ignored since no evidence was found requiring its postulation. Anderson and Lehn[5] have argued that nitrogen inversion in such compounds should be consecutive rather than simultaneous, since simultaneous inversion requires eclipsing of the *N*-alkyl groups. This possibility cannot be excluded in the diazetidines, but one must assume that one of the inversions is fast compared to the other. If this were not the case, one would expect to see peaks due to an axial-equatorial isomer.

Experimental Section

The NMR spectra were recorded on a Varian 56/60 using deuterated chloroform as solvent and Me_4Si as internal standard. All frequencies were calibrated using standard sidebanding techniques. The variable temperature probe was calibrated with methanol at temperatures below 40 °C and with ethylene glycol above 40 °C. Mass spectra were run on a CEC Model 21-104 at 70 eV. Decoupling experiments were done on an HA 100. Boiling points are uncorrected. The IR and far-IR spectra of the described 1,2-diazetidines have been determined as have the pK_b values.[2] These results will be the subject of a separate paper.

1,2-Dimethyl-1,2-diazetidine. Into a flask equipped with a mechanical stirrer, a nitrogen atmosphere, a dry ice condenser, and a dropping funnel were placed 53 g (0.5 mol) of anhydrous sodium carbonate, 100 mL of anhydrous xylene, and 10.2 g (0.17 mol) of 1,2-dimethylhydrazine. The temperature was raised to 100 °C and a solution of 33.5 g (0.18 mol) of 1,2-dibromoethane in 50 mL of anhydrous xylene was added dropwise with stirring over a 4-h period. Heating was continued for an additional 8 h. The reaction mixture was distilled until the temperature reached 110 °C, yielding a two-phase distillate. The top phase was redistilled to give 4.7 g (32%) of the diazetidine: bp 70–72 °C (lit.[20] 70–71 °C); mass spectrum (rel intensity) 86 (100), 71 (30), 56 (15).

1,2-Diethyl-1,2-diazetidine. Using a procedure similar to that above, to 100 g of anhydrous sodium carbonate, 200 mL of anhydrous xylene, and 30 g (0.34 mol) of 1,2-diethylhydrazine[23] at 120 °C was added dropwise with stirring 100 g (1.06 mol) of 1,2-dibromoethane over a period of 8 h. The insoluble salts were removed by filtration and the solution was extracted with 4 N hydrochloric acid. The acid extracts were made basic and the organic layer was extracted with ether. The ether extract was dried over magnesium sulfate and then distilled to give 10.5 g (28%) of the 1,2-diazetidine: bp 119–120 °C; mass spectrum *m/e* (rel intensity) 114 (9), 99 (26), 85 (27), 56 (100).

Anal. Calcd for $C_5H_{14}N_2$: C, 63.11; H, 12.36; N, 24.53. Found: C, 62.89; H, 12.42; N, 24.79.

1,2-Diisopropyl-1,2-diazetidine. The same procedure as for the diethyl compound was used except for a temperature of 130 °C, a 20-h addition time, and a tenfold excess of ethylene bromide. Workup as with the diethyl compound gave 25.2 g (60%) of the diazetidine: bp 37 °C (7 mm) and 154–155 °C (atmospheric pressure)from 34.2 g of 1,2-diisopropylhydrazine;[24] mass spectrum *m/e* (rel intensity) 142 (4), 127 (1), 99 (11), 56 (100).

Anal. Calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N. 19.69. Found: C, 67.79; H, 12.73; N, 19.51.

1,2-Di-*tert*-butyl-1,2-diazetidine. The same procedure was used as for the diethyl compound, except for a reaction temperature of 135 °C, an addition time of 16 h, and a tenfold excess of ethylene bromide. Workup as with the diethyl compound gave 1.1 g (2.3%) of the diazetidine: bp 30–31 °C (4.7 mm) from 40 g of 1,2-di-*tert*-butylhydrazine;[25] mass spectrum *m/e* (rel intensity) 170 (2), 155 (0.2), 113 (1), 56 (100).

1,2-Diisopropyl-3-phenyl-1,2-diazetidine. To 28.5 g (0.25 mol) of 1,2-diisopropylhydrazine, 200 g of anhydrous sodium carbonate, and 650 mL of xylene at 130 °C was added dropwise with stirring a solution of 66 g (0.25 mole) of 1-phenyl-1,2-dibromoethane in 300 mL of anhydrous xylene over a period of 72 h. Workup as with the diethyl compound gave 1.5 g (2.9%) of the diazetidine: bp 105 °C (1 mm); mass spectrum *m/e* (rel intensity) 218 (8), 203 (2), 175 (4), 132 (100).

1,2-Diethyl-3-methyl-1,2-diazetidine. The same procedure as with the diethyl compound was used except that a temperature of 120 °C, an addition time of 16 h, and a threefold excess of 1,2-dibromopropane was used. A yield of 16.5 g (24%) of the diazetidine, bp 25 °C (9 mm), was obtained from 47.3 g of 1,2-diethylhydrazine. The elemental analysis was not satisfactory. Gas chromatography indicated the presence of an impurity. Mass spectrum *m/e* (rel intensity) 128 (58), 113 (18), 99 (88), 70 (100).

Registry No.—1,2-Diethyl-3-methyl-1,2-diazetidine, 66303-61-5; 1,2-dimethylhydrazine, 540-73-8; 1,2-dibromoethane, 106-93-4; 1,2-diethylhydrazine, 1615-80-1; 1,2-diisopropylhydrazine, 3711-34-0; 1,2-di-*tert*-butylhydrazine, 13952-69-7; 1-phenyl-1,2-dibromoethane, 93-52-7; 1,2-dibromopropane, 78-75-1.

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Structure and Reactivity of α,β-Unsaturated Ethers. 16. Electrophilic Addition of Benzenesulfenyl Chloride to α,β-Unsaturated Ethers and Sulfides

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The rates of addition of benzenesulfenyl chloride to α,β-unsaturated ethers and sulfides have been measured in CCl_4 at 30 °C. Reactivities of alkyl vinyl ethers and sulfides increase with the electron donating ability of alkyl group, ρ^* being −5.4 and −1.7, respectively. β-Alkyl and β-methoxy substitutions enhance the reactivity of vinyl ether while α-methyl substitution influences it little. Adducts are exclusively the Markownikoff type. With ethyl propenyl ethers, anti addition is slightly dominant over syn addition. It was concluded from these results that the rate-determining transition state resembles a symmetrically bridged sulfonium ion intermediate **23** and that an open carbonium ion mediates between the rate- and product-determining steps.

It is established that the addition of a sulfenyl halide to an olefin proceeds through an episulfonium ion intermediate to give stereospecifically an anti adduct.[1] One example of a nonstereospecific addition of an arenesulfenyl chloride to an olefin has recently been found with 1-(*p*-alkoxyphenyl)propenes.[2] It was suggested that the rate-determining transition state closely resembles the bridged sulfonium ion even in the latter reaction.

Enol ethers undergo electrophilic attack to give a carbonium ion intermediate stabilized by the direct conjugation with the alkoxy oxygen atom. This conjugative stabilization of an open carbonium ion might make the contribution of a bridged structure unnecessary in the transition state.[3]

In view of these considerations, we have investigated the addition of benzenesulfenyl chloride to various enol ethers as well as vinyl sulfides. Structures of the substrates studied here are shown in Tables II–IV.

Experimental Section

Materials. Benzenesulfenyl chloride (**1**) was prepared from diphenyl disulfide and sulfuryl chloride according to the literature,[4] boiling at 70 °C (10 mm) [lit.[4] 49 °C (4 mm)]. Carbon tetrachloride and carbon disulfide were distilled from P_2O_5. 2,4-Dinitrophenylhydrazine of reagent grade (Wako) was used without further purification.

Commercial ethyl (**3**), *n*-butyl (**6**), and isobutyl vinyl ethers (**7**) were distilled from $LiAlH_4$. Methyl (**2**) and *tert*-butyl vinyl ethers (**5**) were prepared by the alcohol exchange of **3** and **6**, respectively.[5] Isopropyl vinyl (**4**) and other alkenyl alkyl ethers (**9**–**15**) were obtained by the pyrolysis of an appropriate acetal as described previously.[6] Preparations of phenyl vinyl ether (**8**),[7] 1,2-dimethoxyethylene (**16**),[8] alkyl vinyl sulfides (**17**–**20**),[9] and phenyl vinyl sulfide (**21**)[10] were described before. Styrene (**22**) was distilled from *tert*-butylcatechol just before use. Geometric isomers were separated by the distillation through a spinning band column, isomeric purity >96% by VPC.

Kinetic Measurements. All the reactions were carried out at 30.0 ± 0.1 °C in a CCl_4 solution under pseudo-first-order conditions with a 50 times excess of olefin. Each stock solution of an olefin (~0.1 M) and **1** (~0.2 M) in CCl_4 was prepared by weighing. Concentration of **2** was determined spectrophotometrically after hydrolysis (λ 285 nm, acetaldehyde). Three milliliters of an olefin stock solution was thermally equilibrated at 30 °C in a stoppered quartz cuvette inserted in a water-jacketted cell holder. Into the olefin solution was injected 30 μL of a stock solution of **1** with use of a microsyringe. The reaction was monitored by the disappearance of **1** (λ_{max} 390 nm) using a Shimadzu spectrophotometer UV-200.

The fast reactions with **10**–**12** were followed with the use of a stopped flow spectrophotometer Union RA-1100. In this case, a stock solution of **1** was 2×10^{-3} M in concentration.

Pseudo-first-order plots were linear over 80% reactions for all the runs studied. Rate constants are given as averages of at least three measurements.

Reaction of 1 with 3. A solution of 0.1 g of **3** in 0.3 mL of CS_2 was placed in an NMR sample tube and cooled at −78 °C. To this solution was added slowly 0.2 g of **1** in 0.2 mL of CS_2. The temperature of the mixture was raised slowly under spinning on an NMR spectrophotometer JNM-4H-100. The spectra were recorded at −60, −30, and 22 °C. The ^1H NMR spectra showed a gradual formation of the single product with the disappearance of **3**. The spectrum of the product was not changed after 1 week at room temperature. The reaction at room temperature gave the same product spectrum (Table I).

The reaction was also conducted in a greater scale (**1**, 1 g; **3**, 0.5 g; CCl_4, 5 mL) and the reaction product was subjected to the acid-catalyzed hydrolysis. After 5 min of reaction at room temperature, the reaction mixture was shaken with 5 mL of 1 N HCl in 80% aqueous ethanol. Hydrolysis products were treated with 2,4-dinitrophenylhydrazine. There was obtained after recrystallization (95% ethanol) ca. 1 g (ca. 44% yield) of the hydrazone, melting at 94–96 °C. Anal. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.61; H, 3.61; N, 16.87. Found: C, 50.42; H, 3.56; N, 16.83. The results show that the hydrolysis product is phenylthioacetaldehyde.

Reactions of 1 with 8, 17, and 21. These reactions were carried out in an NMR sample tube at room temperature. The ^1H NMR spectra of the reaction mixture showed the formation of the single adduct. The spectral data are given in Table I. The hydrolysis products of the adduct were identified as above. All the adducts gave only phenylthioacetaldehyde as an aldehydic product.

Reactions of 1 with 9c and 9t. The reactions in an NMR sample tube were carried out in the same way as above. The reactions at room temperature resulted in an essentially identical ^1H NMR spectrum both from **9c** and from **9t**. The spectrum showed the formation of two isomeric adducts, the spectra (e) and (t) in Table I, in the ratio of about 4/6.

The sulfenyl chloride **1** was added to the CS_2 solution of **9** at lower temperature. ^1H NMR spectra were recorded with raising temperatures. The reaction mixture obtained from **1** and **9t** showed the ^1H NMR spectra of changing ratio of the adducts (e) and (t); 7.5/2.5 at −60 to −30 °C, 7/3 at 0 °C, and 4/6 at 22 °C. On the other hand, the reaction between **1** and **9c** gave the adducts (e) and (t) in the ratio of 3/7 at −60 to −30 °C which changed to 4/6 at 22 °C.

The mixture of the two adducts (of the ratio 4/6) was subjected to the hydrolysis in the same way as above. The aldehydic product was isolated as 2,4-dinitrophenylhydrazone in ca. 60% yield, mp 105–106.5 °C (95% ethanol). Anal. Calcd for $C_{15}H_{14}N_4O_4S$: C, 52.03; H, 4.04; N, 16.18. Found: C, 51.94; H, 3.97; N, 16.20. The hydrolysis product must be α-phenylthiopropionaldehyde.

Results

Kinetics. The rates of addition of benzenesulfenyl chloride (**1**) to various enol ethers as well as vinyl sulfides were measured in CCl_4 solution in the presence of a large excess of the latter substrate. Pseudo-first-order plots were linear over 80% reactions. The geometric isomer of alkenyl alkyl ethers, which may undergo possible isomerization, was carefully investigated in its kinetic behavior. Both cis and trans isomers showed excellent linearity in their first-order plots during about 4 halflives. This indicates that the geometrical isomerization does not take place during the reaction to affect the rate of addition.

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Table I. NMR Spectra of the Adducts $C_6H_5SCH_2CHCl(XR)$ or $CH_3CH(SC_6H_5)CHCl(XR)$[a]

Substrate No.	Registry no.	XR	δ, ppm (J, Hz) CH_3	CH_2S or CHS	CHCl	R
3	66303-47-7	OC_2H_5		3.33 d (4.5), 3.36 d (8.3)	5.48 dd (4.5, 8.3)	3.75 q, 1.10 t
8	66303-48-8	OC_6H_5		3.35 d (4.1), 3.67 d (7.4)	5.43 dd (4.1, 7.4)	
17	66303-49-9	SCH_3		3.35 d (15.0)	4.93 t (15.0)	2.10 s
21	66303-50-2	SC_6H_5		3.33 d (15)	5.08 t (15)	7.05–7.70 m
9	66303-51-3	OC_2H_5 (e)	1.40 d (7.0)	3.2–3.6 m	5.42 d (4.8)	1.09 t, 3.6–4.0 m
	66303-52-4	(t)	1.46 d (7.0)	3.2–3.6 m	5.62 d (2.1)	1.20 t, 3.6–4.0 m

[a] Solvent: CCl_4.

Table II. Rate Constants for the Addition of 1[a] to Vinyl Ethers, CH_2=CHOR, at 30 °C in CCl_4

No.	Registry no.	R	10^2k_2, M^{-1} s^{-1}
2	107-25-5	CH_3	3.39
3	109-92-2	C_2H_5	10.6
4	18888-46-5	i-C_3H_7	33.6
5	926-02-3	t-C_4H_9	143
6	111-34-2	n-C_4H_9	9.80
7	109-53-5	i-C_4H_9	8.21
8	766-94-9	C_6H_5	0.294
22	52601-97-5	Styrene	0.778

[a] Registry no. 931-59-9.

The pseudo-first-order rate constants k_1 were proportional to the olefin concentration ranging 0.04–0.15 M. That is, the reaction is second order in reactants.

$$\text{rate} = k_1[1]$$

$$\text{rate} = k_2[\text{olefin}][1] \quad (1)$$

The rates were measured in the presence of a small amount of a radical inhibitor, benzoquinone, but the rate constants k_2 obtained were within experimental errors equal to those obtained in its absence. The addition must occur electrophilically but not through a free-radical mechanism.

The second-order rate constants k_2 are summarized in Tables II–IV for vinyl ethers, substituted vinyl ethers, and vinyl sulfides, respectively.

Structure of Adducts. The ^1H NMR spectra of the reaction mixtures with vinyl ethers, **3** and **8**, and vinyl sulfides, **17** and **21**, showed the formation of single product. Each of these reaction products was subjected to acid-catalyzed hydrolysis in 1 N HCl aqueous ethanol. The hydrolysis products were treated with 2,4-dinitrophenylhydrazine. The hydrazone isolated was identified as that of phenylthioacetaldehyde in all the cases examined above.

$$\underset{\text{X = O or S}}{CH_2{=}CHXR} + \underset{1}{C_6H_5SCl} \longrightarrow C_6H_5SCH_2CH\begin{matrix}XR\\Cl\end{matrix}$$

$$\xrightarrow{H_2O} C_6H_5SCH_2CHO + HCl + RXH \quad (2)$$

The product of the addition is no doubt exclusively the Markownikoff-type adduct. The ^1H NMR spectra are consistent with this structure.

In order to examine a possible rearrangement of the initially formed adducts during the addition, the reaction between **1** and **3** was followed carefully on an NMR spectrometer at lower temperatures of −60 °C to room temperature. No incipient signals other than those of the Markownikoff adduct were observed. Furthermore, the spectra were stable over 1 week at room temperature.

The ^1H NMR spectra of the reaction mixture from *cis*- and *trans*-propenyl ethyl ethers, **9c** and **9t**, showed the formation of two isomers of the adduct. Both the isomers give α-phenylthiopropionaldehyde on hydrolysis. That is, the two isomeric adducts obtained must be stereochemical isomers (erythro and threo) of the Markownikoff-type adduct.

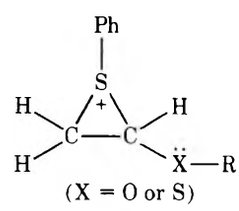
$$\underset{\textbf{9c or 9t}}{CH_3CH{=}CHOC_2H_5} + \underset{1}{C_6H_5SCl} \longrightarrow \underset{\text{erythro and threo}}{C_6H_5S(CH_3)CH{-}CH(OC_2H_5)Cl}$$

$$\xrightarrow{H^+,H_2O} C_6H_5S(CH_3)CHCHO + HCl + C_2H_5OH \quad (3)$$

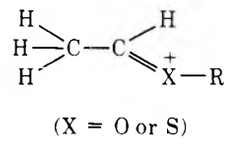
The isomer of greater coupling constant of a CHCl signal (e) may be assigned to that of the erythro configuration and that of smaller coupling constant the threo configuration.[11] Thus, the cis isomer **9c** gave a slightly greater amount of the threo adduct (70%) at a lower temperature of −60 °C while the trans isomer **9t** resulted in the preponderant formation of the erythro isomer (75%) at lower temperature. That is, the anti addition is favored over the syn addition. At higher temperature, however, both **9c** and **9t** gave the same ratio of the erythro and the threo adducts of 4/6. The isomer ratio of the adducts obtained at lower temperature also changed to this ratio (4/6) on the rise of the temperature (to 22 °C), which indicates it to be a thermodynamic equilibrium ratio.

Discussion

The Effects of Alkoxy and Alkylthio Groups. The rate constants given in Tables II and IV show that alkyl vinyl ethers are 3–5 times more reactive than the corresponding sulfides. Such a reactivity difference found in the acid-catalyzed hydrolysis was as great as 10^2–10^4 times.[6,9,12] The rather small difference observed for the present reaction must be due to a smaller contribution for the pπ conjugation involving the O or S lone pair electrons in the transition state like **23**. The carbonium ionlike transition state (**24**) in the hydrolysis owes



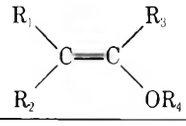
(X = O or S)
23



(X = O or S)
24

its stability greatly to the pπ conjugation. The pπ conjugative stability is attained more effectively with the 2p orbitals of oxygen than with the 3p orbitals of the sulfur atom.[9,10] Such effects must be moderate in the transition state **23**, in which a positive charge resides partly on the sulfenyl S atom.[1] Consequences of these factors are the greater reactivity of the

Table III. Rate Constants for the Addition of 1 to Ethers (at 30 °C in CCl_4)



No.	Registry no.	R_1	R_2	R_3	R_4	k_2, M^{-1} s^{-1}
9c	4696-25-7	H	CH_3	H	C_2H_5	2.03
9t	4696-26-8	CH_3	H	H	C_2H_5	1.12
10c	4188-64-1	H	CH_3	H	i-C_3H_7	4.23
10t	4188-65-2	CH_3	H	H	i-C_3H_7	2.75
11c	10034-12-5	H	C_2H_5	H	CH_3	3.33
11t	10034-13-6	C_2H_5	H	H	CH_3	0.574
12c	4884-01-9	H	C_2H_5	H	C_2H_5	8.57
12t	1528-20-7	C_2H_5	H	H	C_2H_5	1.68
13c	16969-28-1	H	C_2H_5	H	i-C_3H_7	10.6
13t	16969-13-4	C_2H_5	H	H	i-C_3H_7	3.22
14	927-61-7	CH_3	CH_3	H	C_2H_5	1.84
15	926-66-9	H	H	CH_3	C_2H_5	0.117
16c	7062-96-6	H	CH_3O	H	CH_3	2.04
16t	7062-97-7	CH_3O	H	H	CH_3	1.19

Table IV. Rate Constants for the Addition of 1 to Vinyl Sulfides, CH_2=CHSR, at 30 °C in CCl_4

No.	Registry no.	R	10^2k_2, M^{-1} s^{-1}
17	1822-74-8	CH_3	1.03
18	627-50-9	C_2H_5	1.20
19	926-65-8	i-C_3H_7	2.29
20	14094-13-4	t-C_4H_9	3.04
21	1822-73-7	C_6H_5	0.274

Table V. Relative Reactivities of Substituted Vinyl Ethyl Ethers in the Sulfenyl Chloride Addition and the Acid-Catalyzed Hydrolysis

No.	Substituent	Addition	Hydrolysis[a]
3	H	1.0	1.0
15	α-CH_3	1.1	~10^3
9c	*cis*-β-CH_3	19	0.39
9t	*trans*-β-CH_3	11	0.12
14	β,β-$(CH_3)_2$	17	0.03
12c	*cis*-β-C_2H_5	81	0.35
12t	*trans*-β-C_2H_5	16	0.09
16c[b]	*cis*-β-OCH_3	60	2.0×10^{-3} [c]
16t[b]	*trans*-β-OCH_3	35	0.5×10^{-3} [c]

[a] Reference 6. [b] Relative to **2**. [c] Reference 8.

vinyl ethers in electrophilic reactions and the greater reactivity difference between the ether and sulfide in the hydrolysis.

Phenyl vinyl ether (**8**) and sulfide (**21**) showed essentially the same reactivity. Similar results were found in the hydrolysis; **8** is only several times more reactive than **21**.[10] Involvement of the phenyl group in the conjugation may moderate the above stabilization effects of the O and S lone pairs.

The rate constants of alkyl vinyl ethers and sulfides are plotted against Taft's σ* values[13] of alkyl groups in Figure 1. Both alkyl vinyl ethers and sulfides increase in their reactivities in the order $CH_3 < C_2H_5 < i$-$C_3H_7 < t$-C_4H_9, ρ* being −5.4 and −1.7, respectively. The reactivity increases with the increasing electron release of the alkyl group. Similar trends are seen in the data of Table III with alkyl propenyl and butenyl ethers. These results are reasonably understood by the stability of a positively charged transition state **23**, although the ground-state electronic structure deduced from the NMR spectral investigations[9,14] is not straightforward. The absolute magnitude of ρ is greater for the ethers than for the sulfides.

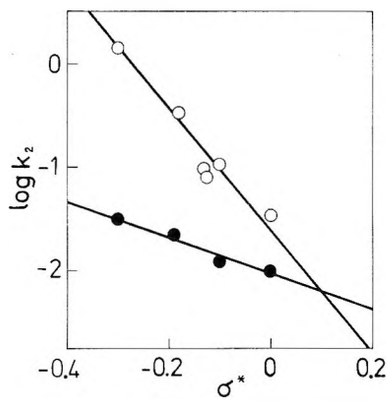


Figure 1. Correlations of the rate constants, k_2, with Taft's σ* values: (○) vinyl ethers; (●) vinyl sulfides.

Similar results were found in the hydrations of alkyl ethynyl ethers[15] and sulfides[16] as well as in the hydrolysis of aryl vinyl ethers and sulfides.[10] The difference in the efficiency of electronic transmission between the O and S atoms may be attributed to their lone pair electrons in 2p and 3p orbitals. Anomalies found in the hydrolysis of alkyl vinyl sulfides ($\rho^* > 0$)[9] were not observed here in the sulfenyl chloride addition.

The Effects of Vinyl Substitution on the Reactivity of Vinyl Ether. The effects of alkyl and alkoxy substitutions of the vinyl hydrogen are found in the data summarized in Table III. The results are compared with those observed for the acid-catalyzed hydrolysis (Table V). A contrasting tendency between the two electrophilic reactions is apparent in Table V. Thus, the β substituents enhance the reactivity in the sulfenyl chloride addition while they reduce the hydrolysis reactivity of vinyl ether.[6] The α-methyl group has little effect on the former while it enhances greatly the latter.[17]

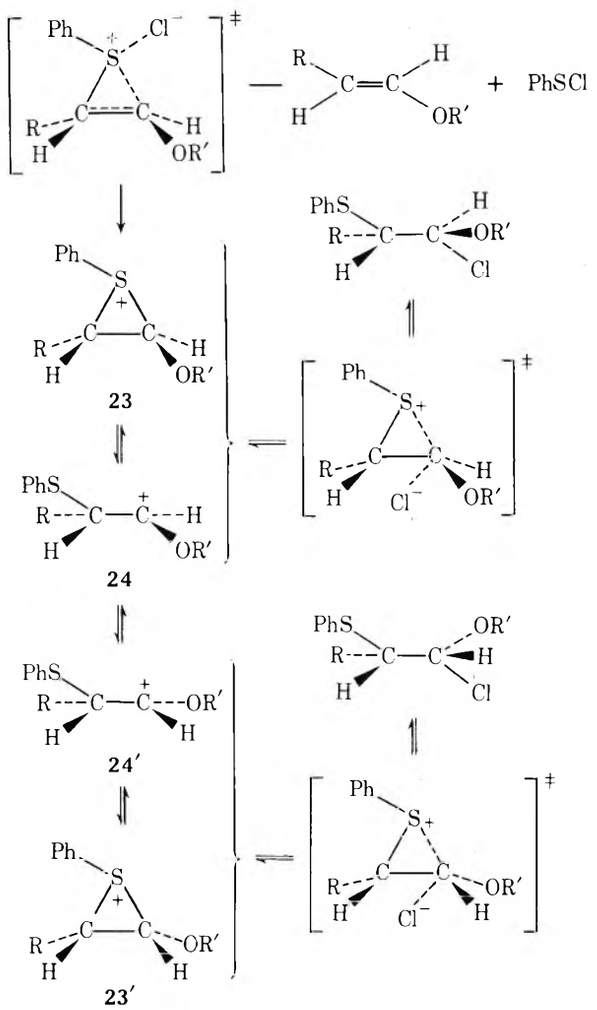
The reactivities in the hydrolysis were rationalized by the relative stabilities of an intermediate carbonium ion like **24**.[6] A β-methyl substitution diminishes the hyperconjugative stabilization of **24**, while an α-methyl substitution enhances it.[6] A β-methoxy group contributes greatly to the stabilization of the ground state but destabilizes the transition state by the inductive electron attraction.[8]

On the contrary, both the alkyl and alkoxy substitutions would increase the stability of the transition state like **23** of the sulfenyl chloride addition by the net electron donation to

the double bond of vinyl ether. In the transition state, the charge transfer interaction between the double bond and the electrophilic sulfenyl sulfur atom must be important to its stability.[18] Small effects of α-methyl substitution may be due to the polarity of the double bond. The charge transfer interaction may be greater with the less polar electron-rich double bond of the β-substituted vinyl ether. In the β,β-disubstituted ether (**14**), a second methyl group seems to have little effect on the reactivity. This would be attributed to the concurrent inverse steric effect. Rate-enhancing effects of alkyl substitutions were previously noted with some alkenes.[19]

With β-monosubstituted vinyl ethers, cis isomers are 1.5–6 times more reactive than the corresponding trans isomers. The greater reactivity of cis isomer in electrophilic additions to olefins has been generally observed with a large variety of olefins and reactions[12,20] and is attributed to the favorable Coulombic interaction between the olefin and the electrophile in the transition state.[12] The present results are new additions to the data of a previously observed trend.

In conclusion, the reactivities of vinyl ethers and sulfides in the sulfenyl chloride addition can be rationalized by assuming a symmetrically bridged transition state like **23**.



Orientation and Stereochemistry of the Addition. The structure of adducts was determined by the hydrolysis experiments and by the ^{1}H NMR spectroscopy. All the adducts were exclusively of the Markownikoff type. Analysis of the adducts from a propenyl ether showed that the anti addition is favored at lower temperatures while the adducts rearrange to the thermodynamic mixture of the erythro and threo isomers at room temperature.

These results indicate that the rotation barrier of an intermediate is not high enough to attain the stereospecificity of addition. As the kinetic results suggested, the transition state of the rate-determining step resembles the bridged sulfonium ion **23**. After this step, an open ion **24** is formed, and the product-determining transition state may be of unsymmetrically bridged structure. This results in the formation of regiospecific (Markownikoff) but nonstereospecific adducts. Whether trapping of the intermediate by chloride ion occurs with a bridged or open ion, **23** or **24**, is not obvious at the present stage although the equilibrium concentration of **23** must be greater than **24**.

Similar observations have recently been made by Schmid and Nowlan[2] with 1-(*p*-alkoxyphenyl)propenes. The present results show more clearly the situation with olefins directly conjugated with an alkoxy group.

Registry No.—Phenylthioacetaldehyde, 66303-55-7; phenylthioacetaldehyde-DNP, 66303-53-5; α-phenylthiopropionaldehyde, 55064-96-5; α-phenylthiopropionaldehyde-DNP, 66303-54-6.

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Electrophilic Additions to Dienes and the 1-Phenylpropenes with Pyridine–Halogen Complexes and Tribromides. Effects on Stereochemistry and Product Ratios

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Dibromide product ratios from bromination with molecular bromine, pyridine–bromine complexes, and tribromide salts for butadiene (**1**), isoprene (**2**), the piperylenes (**3a–b**), the 2,4-hexadienes (**4a–c**), cyclopentadiene (**5**), and the 1-phenylpropenes (**6a–b**) are reported. Bromine chloride addition with analogous reagents to **2, 3a–b,** and **6a–b** is reported. The pyridine–halogen complexes and tribromide give much less 1,4-dihalide product from the dienes than does the molecular halogen. The proportion of 1,4 addition to dienes is suppressed further by an increase in amine concentration. Dienes **4a–b** and alkenes **6a–b,** which give nonstereospecific 1,2 addition with bromine and bromine chloride, approach 100% anti addition when the pyridine–halogen complexes or tribromide is used as the brominating agent. The stereochemistry of 1,4-bromine addition with dienes **4a–c** and **5** is primarily anti in the presence of amine, in contrast to being chiefly syn with molecular halogen in the absence of amine. Possible mechanistic differences between the halogenating agents are suggested.

Crystalline bromine complexes such as pyridine hydrobromide perbromide ($PyHBr_3$), pyridine dibromide ($PyBr_2$), and related amine–dibromides are readily prepared and have advantages over liquid bromine because of ease in handling. Significantly different results between molecular bromine and tribromide have been noted,[1] particularly in the bromination of ketones. Our attention was attracted to the complexes as potentially novel halogenating agents by the proposal that $PyHBr_3$, $PyBr_2$, and PyBrCl add halogen to certain alkenes by a mechanism ($AdEC_2$) in which the nucleophilic step is rate determining,[2] which is in contrast to the commonly accepted halogen addition mechanism,[3] where the formation of a cyclic halonium ion or halo carbonium ion is rate determining ($AdEC_1$). We felt that the above novel proposal could be explored by studying the halogenation of dienes with the halogen complexes. In a preliminary study we reported the addition of bromine chloride to cyclopentadiene, along with several amine–BrCl complexes, and noted striking differences between the two classes of reagents.[4] In particular the amount of 1,4 addition was greatly reduced with the complexes. In this paper we have extended the study to include a variety of dienes and alkenes whose stereochemistry of molecular halogen addition had been reported. The unsymmetrical dienes, isoprene and the piperylenes, were included because differences in bond reactivities between molecular BrCl and BrCl complexes could be determined.

Results

Competition between 1,4 and 1,2 Addition to Dienes. Table I shows the dibromide products[5] obtained from butadiene (**1**), isoprene (**2**), and the piperylenes, *trans*-**3a** and *cis*-**3b.** Dibromides[5] obtained from the 2,4-hexadienes, *trans,trans*-**4a,** *cis,trans*-**4b,** and *cis,cis*-**4c,** and from cyclopentadiene (**5**) are shown in Table II. Product ratios of dibromides obtained with molecular bromination are compared to those obtained with the amine–dibromide complexes, pyridine dibromide ($PyBr_2$), 3,5-lutidine dibromide (3,5-$LuBr_2$), and 2,6-lutidine dibromide (2,6-$LuBr_2$), and the tribromides, pyridine hydrobromide perbromide ($PyHBr_3$) and tetraethylammonium tribromide (Et_4NBr_3).

All of the dienes examined show increases in 1,2 addition when the amine dibromide or a tribromide is substituted for molecular bromine. In fact the 1,2 dibromide is the main product with the latter reagents with all of the dienes except isoprene, whereas with molecular bromine in methylene chloride all of these dienes yield predominately the 1,4-dibromide. Experiments were done to assure that the dibromide products were stable to the reaction conditions.

Data in Tables I and II show that the degree to which 1,4 addition is eliminated by the use of amine dibromides depends upon the concentration of excess amine and also upon the structure of the amine.[6] For example, the ratio of 1,2 to 1,4 addition with butadiene was 5.7 with pyridine dibromide alone and 24 in the presence of a fivefold excess of pyridine. The 1,2 to 1,4 dibromide ratio from isoprene is 0.45, 1.6, and 2.3 for $PyBr_2$, a fivefold pyridine excess, and a tenfold pyridine excess, respectively. Similar increases in 1,2 addition are observed with other amines for **1** and **2** and with dienes **4a,b** and **5** in Table II.

Stereochemistry of 1,2 Addition. Tables II and III present data on the effect of amines and tribromide in changing the stereochemistry of 1,2 and 1,4 addition. Data for the dienes **4a–c** and **5** are shown in Table II and data for the β-methylstyrenes, *trans*-**6a** and *cis*-**6b,** are shown in Table III. Scheme I shows possible stereochemical routes for formation of the products.

Scheme I

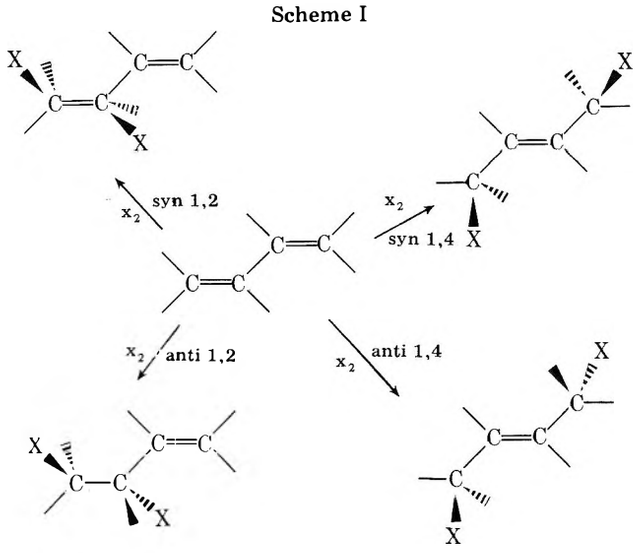

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Table I. Effects of Amines and Tribromides in Bromination of Butadiene, Isoprene, and the Piperylenes

Run	Diene	Registry No.	Brominating[a] agent	Added amine[b] (amine/Br_2)	Dibromides,[c,d] % I	II	III	IV	1,2/1,4 addn.
1	**1**	106-99-0	Br_2		24			76	0.32
2	**1**		$PyHBr_3$		88			12	
3	**1**		$PyBr_2$		85			15	5.7
4	**1**		$PyBr_2$	Py (1:1)	91			9	10
5	**1**		$PyBr_2$	Py (3:1)	95			5	19
6	**1**		$PyBr_2$	Py (5:1)	96			4	24
7	**1**		2,6-$LuBr_2$		71			29	2.4
8	**1**		2,3-$LuBr_2$	2,6-Lu (5:1)	87.5			12.5	7
9	**2**	78-79-5	Br_2		12.5	0.5	4	83	0.15
10	**2**		$PyHBr_3$		46	4.5	2.5	47	
11	**2**		$PyBr_2$		30	1	3	66	0.45
12	**2**		$PyBr_2$	Py (5:1)	58.5	3	1.5	37	1.6
13	**2**		$PyBr_2$	Py (10:1)	65	5	3	27	2.3
14	**2**		2,6-$LuBr_2$		22	0.5	2.5	75	0.29
15	**2**		2,6-$LuBr_2$	2,6-Lu (5:1)	44.5	3.5	2.0	50	0.92
16	**2**		2,6-$LuBr_2$	2,6-Lu (10:1)	50.5	3.5	2.5	43.5	1.17
17	**2**		3,5-$LuBr_2$		27	3	4	71	0.40
18	**2**		3,5-$LuBr_2$	3,5-Lu (10:1)	74	6	1	19	4.0
19[e]	**2**		Br_2	3,5-Lu (10:1)	71	10	2	17	4.3
20[e]	**2**		Br_2	Et_4NBr (5:1)	44.5	7	2.5	46	1.06
21	**3a**	2004-70-8	Br_2		30			70	0.43
22	**3a**		$PyHBr_3$		63	1		36	1.8
23[e]	**3a**		Br_2	Py (5:1)	83.5	1.5		15	5.7
24	**3b**		Br_2		20	0.5		79.5	0.26
25	**3b**		$PyHBr_3$		63.5	8		28.5	2.5
26[e]	**3b**	1574-41-0	Br_2	Py (5:1)	79.5	11.5		9	10

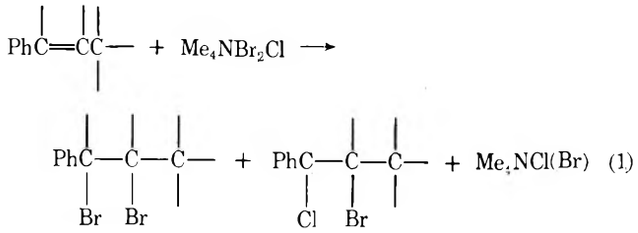
[a] The brominating agent (neat bromine, the solid amine dibromide, or solid pyridine hydrobromide perbromide ($PyHBr_3$)) was added last to a methylene chloride solution of the alkene and amine. The alkene was 0.02 mol fraction, with respect to the solvent. The temperature was 0–5 °C. [b] (Amine/Br_2) is the mole ratio of the amine to moles of available bromine. [c] The dibromides are identified as follows: From **1**, I = 3,4-dibromo-1-butene (Registry no. 10463-48-6) and IV = 1,4-dibromo-*trans*-2-butene (Registry no. 821-06-7); from **2**, I = 3,4-dibromo-3-methyl-1-butene (Registry no. 64251-92-9), II = 3,4-dibromo-2-methyl-1-butene (Registry no. 64251-93-0), III = 1,4-dibromo-2-methyl-*cis*-2-butene (Registry no. 16526-18-4), and IV = 1,4-dibromo-2-methyl-*trans*-2-butene (Registry no. 16526-19-5); from **3a** and **3b**, I = 4,5-dibromo-2-pentene (trans from **3a** (Registry no. 25296-35-9) and cis from **3b** (Registry no. 25356-03-0), II = 3,4-dibromo-1-pentene (erythro from **3a** (Registry no. 25296-34-8) and threo from **3b** (Registry no. 25356-02-9)); IV = 1,4-dibromo-*trans*-2-pentene (Registry no. 25296-22-4). The percentages are normalized to 100%. [d] Yields of total dibromides were determined by NMR on selected runs as follows: 9, 80%; 18, 33%. [e] The diene was added last in these runs to a solution in which bromine and the amine or bromine and tetraethylammonium bromide (run 20) had been allowed to equilibrate for a few minutes.

The 1,2 addition of molecular bromine to dienes **4a–c**[5d] and the alkenes **6a** and **6b**[3,7] previously had been found to be nonstereospecific, i.e., some syn addition was observed. The lack of complete anti addition to the above alkenes was interpreted as meaning that delocalization of positive charge into the neighboring vinylic or benzylic system weakens bridging to bromine and permits an open carbonium ion to form.[7,5d]

The data in Tables II and III show that when amine–dibromides or –tribromides are substituted for molecular bromine a much higher percentage of anti 1,2 addition is observed. For example, addition of solid $PyBr_2$ to the cis alkene, **6b**, results in 98% *threo*-dibromide in contrast to molecular bromination which is only 74% stereospecific. The reaction of **6b** with $PyHBr_3$ gave essentially 100% threo product. The dienes **4a–c** and **5** also show a marked trend in the direction of stereospecific anti addition when the complexes are employed as brominating agents. A further increase in anti addition was obtained when an excess of amine was used (e.g., run 2 vs. run 7 and run 10 vs. run 13, Table II).

The effect (restoration of anti addition) is more pronounced when the solid $PyBr_2$ is added than when the alkene is added last to an equilibrated solution of $PyBr_2$ (runs 2 vs. 3 and 10 vs. 11). In general the tribromides were more effective than dibromides in producing stereospecific 1,2 addition. The above differences can be explained on the basis of dissociation of the complexes (see eq 2, Discussion Section). Once dissolved, $PyBr_2$ would be able to equilibrate to free bromine. The tribromide salt would give less free bromine since its dissociation constant is reported[8] to be much smaller than that of $PyBr_2$.

Similar differences between the molecular halogen and halogen complexes was found with bromine chloride. We found (runs 6, 7, and 8 in Table III) that bromine chloride addition to **6a** and **6b** was nonstereospecific to about the same extent as bromine whereas addition of BrCl via PyBrCl was stereospecific (runs 9 and 10). We also prepared the trihalide salt, tetramethylammonium dibromochloride (Me_4NBr_2Cl) and studied its reaction with **6a** and **6b** (runs 11 and 12). The latter reaction gave both dibromides and bromochlorides (see eq 1) and the addition of each was nearly 100% stereospecific.



(1)

Stereochemistry of 1,4 Addition. The stereochemistry of 1,4 addition of bromine to dienes **4a–c** and **5** (see Scheme I) was previously examined.[5d] We reported that, although the 1,4 addition was nonstereospecific, there was a strong preference for syn addition. The data in Table II show that along with the total reduction in 1,4 (vs. 1,2) addition which occurs when the amine–dibromides and tribromide are substituted

Table II. Effects of Amines and Tribromide on Stereochemistry of 1,2- and 1,4-Bromine Addition to Dienes

Run	Diene	Brominating agent[a]	Added amine or salt[b]	Dibromides,[c,d] % Anti 1,2	Syn 1,2	Anti 1,4	Syn 1,4	1,2 addn. % anti	1,4 addn. % syn	1,2/1,4 addn.
1	**4a**[h]	Br_2	None	19.5[l]	4.5[m]	15[n]	61[o]	81	80	0.32
2	**4a**	$PyBr_2$	None	45	5.5	16	33.5	89	68	1.02
3	**4a**	$PyBr_2$[e]	None	67	4	13.5	15.5	94	53	2.45
4	**4a**	$PyHBr_3$	None	59.5	5	10	25.5	92	72	1.82
5	**4a**	Br_2	Et_4NBr (1:1)	93	1.5	3.5	2	98	36	17
6	**4a**	Br_2	Et_4NBr (1:5)	97	1	1.5	0.5	99	40	49
7	**4a**	$PyBr_2$	Py (1:5)	89	3	4.5	3.5	97	44	11.5
8	**4a**	3,5-$LuBr_2$	3,5-Lu (1:20)	92.5	4	2	1.5	96	43	28
9	**4b**[f,i]	Br_2	None	17.5	4	15.5	62	81	80	0.28
10	**4b**[f]	$PyBr_2$	None	51	4	14.5	26	93	64	1.47
11	**4b**[f]	$PyBr_2$[e]	None	74.5	1	11.5	9.5	98	45	3.8
12	**4b**[f]	$PyHBr_3$	None	63	2	12	19.5	97	62	2.2
13	**4b**[f]	$PyBr_2$	Py (1:5)	70.5	1	9.5	10	99	51	4.1
14	**4b**[f]	3,5-$LuBr_2$	3,5-Lu (1:20)	77		7	2	100	22	10
15	**4c**[j]	Br_2	None	14[p]	5[q]	5	76	74	94	0.23
16	**4c**	3,5-$LuBr_2$	3,5-Lu (1:20)	97.5		1.5	1	100	40	39
17	**5**[k]	Br_2	None	23.5[r]	*g*	14[s]	51[t]	*g*	78	0.54
18	**5**	Br_2	Py (1:1)	66	*g*	18	14	*g*	44	2.1
19	**5**	Br_2	Py (1:20)	88.5		8	3.5	100[u]	30	7.7
20	**5**	Br_2	3,5-Lu (1:20)	97		2	1	100	33	32
21	**5**	Br_2	Et_4NBr (1:1)	60.5	*g*	20.5	17.5	*g*	54	1.63
22	**5**	Br_2	Et_4NBr (1:5)	79		10.5	10.5	100	50	3.8

[a] The reaction conditions are the same as reported in Table I except that unless otherwise stated the diene was added last to a solution of the brominating agent (and amine, if added) which had been allowed to equilibrate for a few minutes. [b] The ratio in parentheses shows the mole ratio between available bromine and the amine or bromide salt. [c] See ref 5d for identification of the dibromides. [d] Percentages are normalized to 100%. Yields of total dibromides were determined by NMR on selected runs as follows: 1, 96%; 6, 107%; 8, 35%; 17, 71%; 20, 62%. [e] The solid $PyBr_2$ complex was added last to the solution of alkene. [f] The difference between the total dibromide percentages and 100% equals the percentage of 4,5-dibromo-*cis*-2-hexene which results from bromination of the trans bond in **4b**. [g] In runs 17, 18, and 21 there is an additional VPC peak in the bromination product in the amount 11.5, 1, and 1.5%, respectively, which was overlooked in our previous investigation of the bromination of **5**. We suspect that this compound may be *cis*-3,4-dibromocyclopentene but were unable to isolate the compound in sufficient amounts to prove its structure. A very dilute solution of the compound (along with about 50% of the other dibromides) was prepared from VPC collection. Upon standing at room temperature in the light for a day, the unknown peak in the above solution largely disappeared. However, significant increase of the other dibromide peaks (determined with an internal standard) did not accompany the loss of the unknown. [h] Registry no. 5194-51-4. [i] Registry no. 5194-50-3. [j] Registry no. 6108-61-8. [k] Registry no. 542-92-7. [l] Registry no. 42086-57-7. [m] Registry no. 42086-58-8. [n] Registry no. 42086-59-9. [o] Registry no. 66323-08-8. [p] Registry no. 42086-55-5. [q] Registry no. 42086-56-6. [r] Registry no. 66323-09-9. [s] Registry no. 42086-50-0. [t] Registry no. 17040-70-9. [u] Registry no. 42086-51-1.

Table III. Addition[a] of Bromine and Bromine Chloride to *cis*- and *trans*-β-Methylstyrenes in CH_2Cl_2

Run	Alkene	Reagent	Dibromides[b] Threo	Erythro	Bromochlorides[b] Threo[c]	Erythro[d]
1	**6a**[f]	Br_2	11[h]	89[i]		
2	**6b**[e]	Br_2	74.5	25.5		
3	**6a**	$PyBr_2$	2	98		
4	**6b**[g]	$PyBr_2$	98	2		
5	**6b**	$PyHBr_3$	100			
6	**6a**	BrCl			8.5[j]	91.5[k]
7	**6b**	BrCl (CCl_4)			75.5	24.5
8	**6b**	BrCl			79	21
9	**6a**	PyBrCl				100
10	**6b**	PyBrCl			100	
11	**6a**	Me_4NBr_2Cl		71		29
12	**6b**	Me_4NBr_2Cl	71.5	0.5	28	

[a] The reaction conditions are the same as those in Table I. The halogenating agent was added last to a solution of the alkene. [b] Product percentages are normalized to 100%. VPC response factors were determined for a dibromide isomer and a bromochloride isomer and were used to establish the mole ratio between dibromides and bromochlorides. Yields of products were determined by VPC and/or NMR and did not drop below 60% for any runs. [c] *threo*-2-Bromo-1-chloro-1-phenylpropane (**7**). [d] *erythro*-2-Bromo-1-chloro-1-phenylpropane (**8**). [e] Fahey and Schneider[3] report 74% threo and 26% erythro for the bromination of **6b** in methylene chloride. [f] Registry no. 873-66-5. [g] Registry no. 766-90-5. [h] Registry no. 21087-20-7. [i] Registry no. 21087-19-4. [j] Registry no. 66323-24-8. [k] Registry no. 4962-44-1.

for bromine, there is an accompanying decrease in the preference for syn-1,4 addition. Thus, the percentage of syn-1,4 addition drops from 80 to 68 for **4a** and from 80 to 64 for **4b** when the brominating agent is changed from neat bromine to a solution of pyridine dibromide (diene added last). Direct addition of the solid complex (runs 3 and 11) causes a greater reduction in the percentage of syn addition. Tribromides reduce the percentage of syn-1,4 addition in a similar manner as do the pyridine dibromides. When the dienes are added to bromine solutions containing an excess of amine (compared to bromine) the small amount of accompaning 1,4-dibromide (runs 7, 8, 13, 14, 16, 18, 19, and 20) usually contains an excess of the anti adduct.

Addition of Bromine Chloride to Dienes 2, 3a, and 3b. The results for bromine chloride addition to the dienes **2, 3a,** and **3b** using the molecular halogen itself and amine solutions of bromine chloride are presented in Table IV. The use of the unsymmetrical electrophile with these dienes permits the ratio of attack at each bond to be determined. Although the presence of amine caused a marked decrease in the amount of 1,4 addition, the relative reactivities of the two double bonds did not change drastically.

It should also be pointed out that the relative reactivities of the two double bonds in **2, 3a,** and **3b** are in line with those reported for a rather different electrophilic system (MeOCl or Cl_2 in methanol).[9]

Discussion

A satisfactory mechanistic interpretation of our data should

Table IV. The Reaction of Bromine Chloride with Isoprene and *cis*- and *trans*-1,3-Pentadiene in CH_2Cl_2 at 25 °C

Run	Diene	Added amine (amine/BrCl)	Bromochloride products, %[a] I	II	III	IV	III + IV
1	**2**	None	15.5	1	10	73.5	83.5
2	**2**	Py (5:1)	53.5	7	8.5	31	39.5
3	**2**	3,5-Lu (5:1)	58	8			34
4	**2**	2,6-Lu (5:1)	48.5	6			45.5
5	**3a**	None	38	0.5	60	1.5	61.5
6	**3a**	Py (1:1)	67	1			32
7	**3a**	Py (5:1)	68	1.5	30	0.5	30.5
8	**3a**	3,5-Lu (5:1)	81	1.5			17.4
9	**3a**	2,6-Lu (5:1)	74.5	1	23	1.5	24.5
10	**3b**	None	31.5	3.5	59.5	5.5	65
11	**3b**	Py (1:1)	67	10.5			22.5
12	**3b**	Py (5:1)	71.5	14.5	12	2	14
13	**3b**	3,5-Lu (5:1)	73.5	18.5			8
14	**3b**	2,6-Lu (5:1)	74.5	10.5			15

[a] The products are identified as follows: from **2**, I = 4-bromo-3-chloro-3-methyl-1-butene (Registry no. 66323-15-7) (**9**), II = 4-bromo-3-chloro-2-methyl-1-butene (Registry no. 66323-14-6) (**10**), III = 4-bromo-1-chloro-2-methyl-2-butene (Registry no. 66323-16-8) (**11**), IV = 1-bromo-4-chloro-2-methyl-2-butene (Registry no. 6323-17-9) (**12**); from **3a** and **3b**, I = 5-bromo-4-chloro-2-pentene (trans (Registry no. 66323-18-0) (**13**) from **3a** and cis (Registry no. 66323-19-1) (**14**) from **3b**), II = 4-bromo-3-chloro-1-pentene (erythro (Registry no. 66323-20-4) (**15**) from **3a** and threo (Registry no. 66323-21-5) (**16**) from **3b**), III = 4-bromo-1-chloro-*trans*-2-pentene (Registry no. 66323-22-6) (**17**), and IV = 1-bromo-4-chloro-*trans*-2-pentene (Registry no. 66323-23-7) (**18**). Product percentages are normalized to 100%. Total product yields, determined by means of VPC internal standards, varied between 69 and 100%.

be able to account for the following differences between additions employing the halogen complexes, amine dibromides and tribromide salts, and those of the free, molecular halogens: (1) Alkenes which give nonstereospecific 1,2 addition with free bromine (**4a–c**, and **6a,b**) and free bromine chloride (**6a,b**) give nearly stereospecific anti addition with the halogen complexes. (2) Conjugated dienes show greatly diminished 1,4 addition with the complexes in comparison to the free halogens. (3) The results with the amine dibromides are very similar to those with the trihalides, especially when an excess of amine is used.

First of all, we want to comment about our observations (Tables I and II) that the effects of the amines depend upon their concentration and structure. A reasonable explanation for the concentration effect is that the pyridine dibromide complexes are in equilibrium with free bromine

$$\text{Py:Br:Br} \rightleftharpoons \text{Py} + \text{Br:Br} \qquad (2)$$

Thus the addition of excess amine suppresses the concentration of molecular bromine.

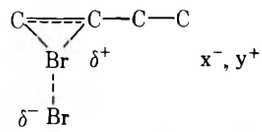
An alternative explanation for the effect of excess amine is that some other equilibrium involving amine is present, such as in eq 3.[10,11] In the latter case, tribromide ion might be the electrophile at high amine concentration.

$$2\text{PyBr}_2 \rightleftharpoons \text{Py}_2\text{Br}^+, \text{Br}_3^- \qquad (3)$$

The similarity in effects which have been observed between amine–dibromides and ammonium–tribromides could therefore be due to the fact that both brominate via tribromide ion or that both reagents simply limit the concentration of free bromine (see later discussion).

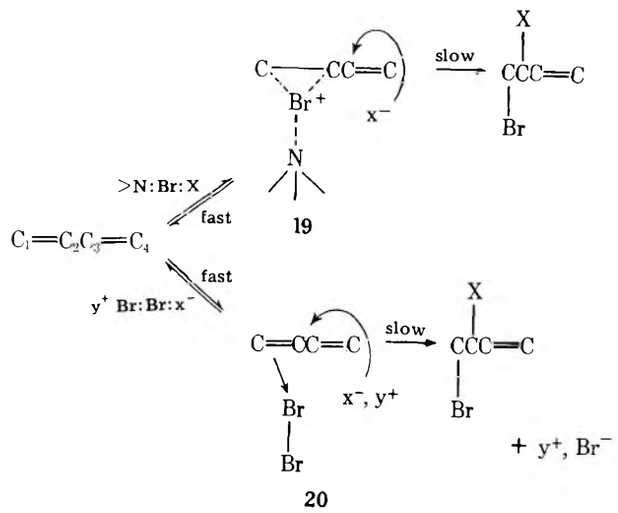
The three amines which were used differ in their capacity to suppress 1,4 addition of bromine to the dienes. In bromination of **1**, $PyBr_2$ gives 85% 1,2-dibromide compared to 71% with 2,6-$LuBr_2$ and with a fivefold excess of each amine, the percentages of 1,2-dibromide are 96 and 87.5, respectively (Table I). In bromination of **2** the effectiveness of the amines in suppressing 1,4 addition varies in the order 3,5-Lu > Py > 2,6-Lu (Table I). The differences between these amines are probably due to the relative stabilities of their bromine complexes and therefore the extent to which each dissociates into free bromine as discussed above.[12,13]

We turn now to a mechanistic discussion of the differences between molecular halogens and their amine and tribromide complexes. One possible explanation for these differences is that there is a fundamental mechanistic change, similar to that proposed by Bellucci[2] for his work on *tert*-butylcyclohexenes, involving a type $AdEC_1$ addition mechanism with the free halogens and a type $AdEC_2$ with the complexes. As shown in Scheme II, the $AdEC_2$ mechanism would involve a rate-determining attack by halide ion on a bromonium–amine complex (**19**) derived from the amine–dibromide[2] or on the alkene–halogen charge transfer complex (**20**) obtained from the trihalide.[14–16] Conceivably both intermediates **19** and **20** are charge-transfer complexes or perhaps **20** could be viewed as a bromonium ion with significant charge on carbon, e.g.,



Intermediates **19** and **20** are similar in that both have a nucleophile (>N: or $Br:^-$) associated with the electrophilic bromine in the intermediate thus reducing the extent to which the positive charge would be localized on the carbon atoms and

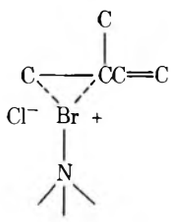
Scheme II



also permiting reversibility of intermediate formation ($AdEC_2$).

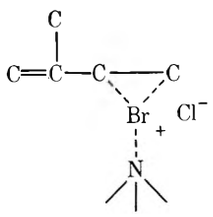
Scheme II can be used to account for some of our observations. Since **19** and **20** are π complexes or bromonium ions with a smaller amount of charge on carbon, they would be expected to yield anti products when attacked by halide ion. Also, with minimal concentration of charge on carbon, charge dispersal to the number 4 carbon of the neighboring vinylic system would be diminished and, hence, 1,4 addition would be reduced. It is not clear why 1,4 addition becomes more anti than syn. Possibly the preferred stereochemistry of S_N2' attack is anti and that what we are seeing is a change from a S_N1' mechanism (molecular halogenation, $AdEC_1$) to a more pure S_N2' mechanism (halogenation with the complexes, $AdEC_2$).[17]

Although Scheme II accounts for some of the facts of this study, it seems questionable at other points. For example, if the mechanisms of Scheme II are operative, we might expect that the products formed from the unsymmetrical dienes, **2** and **3a,b,** might show considerable differences between molecular bromine chloride and the pyridine complexes. In the case of 2,6-$LuBr_2$ considerable steric hindrance should be experienced for attack on the 3,4 bond in **3a** and **3b** and the 1,2 bond in **2.** Yet we see no significant diminution in the relative amount of attack on the more highly substituted double bond in going from BrCl to 2,6-$LuBr_2$. We would expect that this would be particularly noticeable in attack on the 1,2 bond in **2,** where attack by halide on the intermediate **19** would require nucleophilic substitution on a tertiary carbon (structure **21**).



21

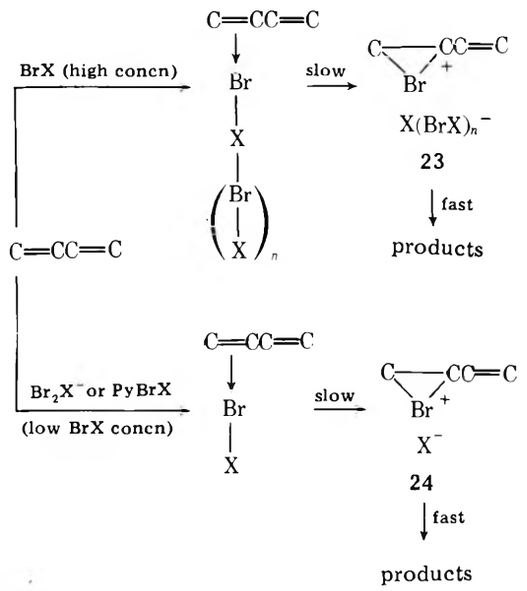
Again we observe no significant decrease in attack at the 1,2 bond when the amine–bromochlorides are the reagents. Indeed there is relatively more 1,2 addition (in comparison to 1,4 addition) resulting from attack on the intermediate **21** than from the intermediate obtained from attack at the 3,4 bond of **2,** i.e., structure **22** (compare runs 1 and 2, Table IV).



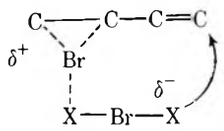
22

In our opinion the data presented here do not provide conclusive evidence either for or against an $AdEC_2$ mechanism in the reaction of the amine–dibromides and –tribromide. Let us suggest another possible explanation for the results obtained with these reagents.[18] Perhaps the differences between the reaction of free halogens and the halogen complexes result from the fact that with the molecular halogens two or more halogen molecules participate in the transition state (second order), whereas reactions with the halogen complexes limit the availability of halogen and impose a first-order mechanism. In other words, the function of the complexes (amine–dibromides and –tribromide) would be to limit the concentration of free halogen. The two mechanisms are compared in Scheme III.

Scheme III



The structures of the anions in the intermediates (**23** and **24**) constitute the real differences between the mechanisms. Whereas in **23** the anion would be a trihalide or polyhalide, in **24** it would be a simple halide ion. Therefore, ion-pair **24** should be much less stable than ion-pair **23** and would quickly collapse to the anti-1,2 adduct before opening of the bromonium ion could occur. The greater stability of the anion in **23** would result in an ion pair of longer lifetime, thus permiting bromonium ion ring opening and the accompanying syn-1,2 addition. Possibly the differences between the anions could account for the large amounts of syn-1,4 addition with the molecular halogen. The complex anion in **23** may interact with the number 4 carbon atom simultaneously with the development of the bromonium ion (structure **25**). On the other hand, the highly unstable character of ion-pair **24** and the relatively small size of the anion might prevent it from yielding much 1,4 adduct.



25

Attempts to test our hypothesis that product ratios are affected significantly by halogen concentration have not been encouraging. In a series of experiments on bromination of the 2,4-hexadienes we found that the use of very dilute bromine did indeed have a striking effect on product compositions in the same manner as the complexes, i.e., stereospecific anti-1,2 addition, greatly reduced 1,4 addition, and lower proportion of syn-1,4 addition. However, the effects were observed only when the solvent was carbon tetrachloride or pentane. There was very little detectable effect of dilution in the more polar solvents, methylene chloride and nitromethane. When bromination of β-methylstyrene was attempted with very dilute bromine, the rate of reaction decreased enormously and there was little change in the stereoselectivity (compared to more concentrated bromine).

Definitive answers to the mechanistic questions raised here may await kinetic studies since little kinetic work has been done in the aprotic, nonpolar solvents in which electrophilic additions are often done.

Finally, we would suggest that results presented here can be used to advantage in synthesis, since the proper selection of halogenation conditions permits isolation of a variety of

pure isomers. For example, the 1,4-dibromide of butadiene is easily obtained by bromination with neat bromine in dichloromethane (followed by crystallization), whereas the 1,2-dibromide can be isolated in high purity when the amine–dibromide or –tribromide is used. Also, essentially pure 1,2-dibromide stereoisomers, e.g., from the 1-phenylpropenes or 2,4-hexadienes, are obtained under the latter bromination conditions. Tribromides, e.g., Et_4NBr_3 which is easily prepared in situ (see footnote *e*, Table I), afforded much higher yields than did the amine–dibromides.[19]

Experimental Section

The alkenes and dienes were obtained commercially and distilled before use. The amines and solvents were used without further purification. The amine–dibromides were prepared by the method described by Bellucci.[2a] Pyridine hydrobromide perbromide ($PyHBr_3$) was prepared by the Fieser method.[1a]

Tetramethylammonium dibromochloride (Me_4NBr_2Cl) was prepared from tetramethylammonium chloride by an adaptation of the procedure used to make $PyHBr_3$. Its melting point was 59–65 °C.

Brominations of Dienes 1, 2, 3a,b, 4a–c, 5. The specific conditions for bromination of the dienes are described in Tables I and II. A typical reaction (run No. 6, Table I) follows: To a mixture of 0.15 mL (0.0015 mol) of isoprene and 0.15 mL (.0019 mol) of pyridine in 4.7 mL (0.073 mol) of dichloromethane at 0–5 °C there was added with stirring 0.089 g (0.00037 mol) of solid pyridine dibromide. After 5 min the reaction mixture was extracted with cold, 10% hydrochloric acid and then shaken with sodium bicarbonate solution. The HCl extraction was done in all runs in which amine was present in the product.

The analysis of the dibromide mixtures was done by VPC as described previously,[5a-d] except that glass columns were used instead of stainless steel.

Yields were obtained on selected runs by NMR after stripping of the solvent and unreacted diene (benzene was used as internal standard).

To assure that the product compositions were uneffected by the reaction conditions, i.e., were kinetically determined, certain control experiments were performed. The absence of reactions between the amines and dibromide products is shown by the following experiment (also done on the bromination product from **4a**): The dibromide mixture from bromination of **2** (run 9, Table I) was stirred with a tenfold excess of 3,5-lutidine for 5 min under the conditions of the typical reaction described above. After removal of the amine by HCl extraction, the product was analyzed by VPC and was found to be the same as before treatment with the amine. The quantity of dibromide was reduced by 22% (NMR) but this may be attributed in part to loss in the extraction and solvent stripping procedure. A similar experiment with the dibromide product (run 1, Table II) of **4a** using a 20-fold excess of 3,5-lutidine showed no effect on the dibromide composition within experimental error.

Control experiments were performed on the dibromide products from **2** and **4a**, similar to those reported previously,[5d] which showed that the dibromides were not rearranged under the conditions of molecular bromination.

Additions to 1-Phenylpropenes (6a,b). The reaction conditions are described in Table I. Mixtures of *erythro*- and *threo*-dibromides were analyzed by VPC and/or NMR as reported previously.[3,7] *threo*-2-Bromo-1-chloro-1-phenylpropane (**7**) and *erythro*-2-bromo-1-chloro-1-phenylpropane (**8**) were separated from each other and from the *erythro*- and *threo*-dibromides by VPC (2.5% SE-30 on 60–80 CW (DMCS), 6 ft × 0.25 in. ss, 100 °C). Retention times for **7**, **8**, the *erythro*-dibromide, and the *threo*-dibromide are respectively 25.2, 22.4, 36.0, and 40.2 min. Pure samples of **7** and **8** were obtained by reaction of the respective alkenes with PyBrCl followed by fractionation. The NMR spectra (Varian T-60, in CCl_4) follow: **7**, 1.88 (d, 3, CH_3, J_{23} = 6.4 Hz), 4.33 (d of q, 1, CHBr, J_{12} = 9.0, J_{23} = 6.4 Hz), 4.90 (d, 1, CHCl, J_{12} = 9.0 Hz), 7.32 [m (narrow), 5, C_6H_5]; **8**, 1.62 (d, 3, CH_3, J_{23} = 6.4 Hz), 4.42 (d of q, 1, CHBr, J_{23} = 6.4, J_{12} = 6.0 Hz), 5.03 (d, 1, CHCl, J_{12} = 6.0 Hz), 7.33 [m (narrow), 5, C_6H_5].

Reaction of Isoprene (2) with Bromine Chloride. The reactions were done at 25 °C, with the diene at 0.02 mol fraction with respect to the solvent dichloromethane. In the reactions using excess amine, the diene was added last to a solution of the amine and bromine chloride. A typical reaction follows: Pyridine (0.58 g 0.0073 mol) and 1 mL of 1.4 M (0.0015 mol) bromine chloride solution (in CCl_4) were dissolved in 12 mL of dichloromethane and a solution of 0.50 g (0.0073 mol) of **2** in 12 mL of dichloromethane was added rapidly with stirring. After 5 min the solution was extracted with cold, 10% hydrochloric acid. Control experiments with excess amine as described for **2** and **4a** above did not effect the bromochloride mixture.

Mixtures of the bromochlorides from **2** were analyzed by VPC under the following conditions: 3% OV-17 on 80–100 CW (DMCS), 70 °C, 6 ft × 0.25 in., ss. Retention times of **9**, **10**, **11**, and **12** are respectively 6.5, 8.5, 32, and 32 min.

The pure bromochlorides were obtained as follows and identified by their NMR spectra reported below. Peaks 1 and 2 (**9** and **10**) were separated and collected by VPC (OV-17). Compound **12** was obtained by recrystallization from a crude reaction product (reaction of **2** with $BrCl$–CCl_4) from pentane at low temperatures. Isomer **11** was obtained via the following independent synthesis:

$$2 \xrightarrow{\text{HOCl (ether)}^{20}} \xrightarrow{PBr_3{}^{21}} \mathbf{11}$$

The crude mixture obtained from this sequence was distilled and **11** was obtained from the mixture by VPC collection (5% DC-550). The compound obtained (**11**) in this way had very similar (but different) NMR spectrum to **12**. Mixtures of **11** and **12** could not be separated by VPC on liquid phases such as SE-30, FFAP, DEGS, dinonyl phthalate, and β,β-dioxypropionitrile. The determination of ratios of **11** and **12** produced in reaction mixtures was accomplished by VPC collection of peak 3 (**11** and **12**) and then analysis by 100 MHz NMR which separated the up-field line of the C_4 methylene doublet of **11** from the other methylene absorptions of **11** and **12**.

The NMR (60 MHz, CCl_4) spectra of the bromochlorides from **2** follow: **9**, 1.80 (s, 3, CH_3), 3.63 (s, 2, CH_2Br), 5.1–5.5 (m, 2, C=CH_2), 5.98 (dd, 1, CH=CH_2, J_{12} = 16.4, $J_{12'}$ = 10.4 Hz); **10**, 1.82 [s (br), 3, CH_3], 3.42–3.72 (m, 2, CH_2), 4.50 (dd, 1, CHCl, J = 5.0, J' = 9.6 Hz), 4.93–5.20 (m, 2, C=CH_2); **11**, 1.87 (s, 3, CH_3), 3.83 (d, 2, CH_2Br, J_{34} = 8.6 Hz), 4.00 (s, 2, CH_2Cl), 5.83 (t, 1, C=CH, J_{34} = 8.6 Hz); **12**, 1.87 (s, 3, CH_3), 3.93 (s, 2, CH_2Br), 4.02 (d, 2, CH_2Cl, J_{34} = 7.2 Hz), 5.79 (t, 1, C=CH, J_{34} = 7.2 Hz).

Reaction of the Piperylenes (3a and 3b) with Bromine Chloride. The reaction conditions are the same as for **2** described above. The mixtures of piperylene bromochlorides were analyzed by VPC [2.5% SE-30 on 80–100 CW (DMCS), 5 ft × 0.25 in. ss, 70 °C] with retention times of 3.8, 4.6, and 6.6 min for (**13** and **14**), (**15** and **16**), and (**17** and **18**), respectively. Pure isomers were identified by their NMR spectra reported below. Pure compounds were obtained from reaction mixtures rich in a particular isomer. Pure **14** was isolated by fractional distillation (bp 50 °C (7 Torr)). Isomers **13**, **15**, **16**, and **18** were isolated by VPC collection (SE-30 or DC-550). Compound **17** was synthesized from **3a** by the procedure used to prepare **11** as described above and was obtained pure by VPC collection.

Since attempts to separate the 1,4 adducts (**17** and **18**) were unsuccessful the ratio between the two was obtained as follows: Peak 3 containing **17** and **18** was collected by VPC (5% DC-550) from a particular reaction mixture. Since the methyl groups absorb in the NMR at 1.80 and 1.57 ppm for **17** and **18**, respectively, their ratio could be obtained. However, small amounts of 4,5-dibromo-2-pentene, a consistent impurity in the bromine chloride reaction, also absorbed at 1.80 ppm. Its composition in the mixture was determined by VPC and its NMR integration was subtracted from that of **17**.

The NMR spectra of the bromochlorides from **3a** and **3b** (60 MHz, CCl_4) follow: **13**, 1.77 (d, 3, CH_3, J_{12} = 5.2 Hz), 3.40 (dd, 1, BrCH(H), J_{45} = 9.0, $J_{55'}$ = 10.0 Hz), 3.65 (dd, 1, BrCH(H), $J_{45'}$ = 5.0, $J_{55'}$ = 10.0 Hz), 4.42 (ddd, 1, CHCl, $J_{45'}$ = 5.0, J_{45} = 9.0 Hz), 5.22–6.0 (m, 2, CH=CH); **14**, 1.75 (d, 3, J_{12} = 5.2 Hz), 3.42 (dd, 1, BrCH(H), $J_{4,5}$ = 8.8, $J_{5,5'}$ = 10.0 Hz), 3.67 (dd, 1, BrCH(H), $J_{45'}$ = 5.2 Hz, $J_{55'}$ = 10.0 Hz), 4.87 (ddd, 1, CHCl, $J_{45'}$ = 5.0, J_{45} = 9.2, J_{34} = 9.2 Hz), 5.18–5.90 (m, 2, CH=CH); **15**, 1.82 (d, 3, CH_3, J_{45} = 6.4 Hz), 3.9–4.5 (m, 2, CHBrCHCl), 5.13–6.0 (m, 3, CH=CH_2); **16**, 1.70 (d, 3, CH_3, J_{45} = 6.4 Hz), 4.28 (d of q, 1, CHBr, J_{45} = 6.4, J_{34} = 3.6 Hz), 4.58 (dd, 1, CHCl, J_{34} = 6.6, J_{23} = 6.6 Hz), 4.22–5.53 (m, 2, C=CH_2), 5.73–6.33 (m, 1, CH=C); **17**, 1.80 (d, 3, CH_3, J_{45} = 6.6 Hz), 3.98 (apparent d, 2, J_{12} = 6.0 Hz), 4.53 (apparent quintet, 1, CHBr, $J_{4,5}$ = 6.5 Hz), 5.62–6.00 (m, 2, CH=CH); **18**, 1.57 (d, 3, CH_3, J_{45} = 6.4 Hz), 3.73–3.93 (m, 2, CH_2), 4.23–4.67 (m, 1, CHCl), 5.63–5.92 (m, 2, CH=CH).

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Registry No.—Br_2, 7726-95-6; $PyHBr_3$, 66323-10-2; $PyBr_2$, 6081-86-3; 2,6-$LuBr_2$, 35120-69-5; 3,5-$LuBr_2$, 35120-70-8; Py, 110-86-1;

2,6-Lu, 108-48-5; 3,5-Lu, 591-22-0; Et_4NBr, 71-91-0; BrCl, 13863-41-7; $BrCl(CCl_4)$, 66323-11-3; PyBrCl, 21300-57-2; Me_4NBr_2Cl, 66323-12-4; Et_4NBr_3, 66323-13-5.

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(1) (a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, pp 967–970, and references therein; (b) V. W. Armstrong, N. H. Chishti, and R. Ramage, *Tetrahedron Lett.*, 373 (1975); (c) D. V. C. Avang and S. Wolfe, *Can. J. Chem.*, **47**, 706 (1969).

(2) (a) P. L. Barili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **37**, 4353 (1972); (b) P. L. Varili, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *ibid.*, **38**, 3472 (1973); (c) G. Bellucci, G. Ingrosso, F. Marioni, E. Mastrorilli, and I. Morelli, *ibid.*, **39**, 2562 (1974).

(3) E.g., see R. C. Fahey and H. J. Schneider, *J. Am. Chem. Soc.*, **90**, 4429 (1968), and references therein.

(4) V. L. Heasley, C. N. Griffith, and G. E. Heasley, *J. Org. Chem.*, **40**, 1358 (1975).

(5) The kinetically determined dibromide products of these dienes have been determined previously. From **1**, (a) V. L. Heasley, G. E. Heasley, R. A. Loghry, and M. R. McConnell, *J. Org. Chem.*, **37**, 2228 (1972); L. F. Hatch, P. O. Gardner, and R. E. Gilbert, *J. Am. Chem. Soc.*, **81**, 5943 (1956). From **2**, (b) V. L. Heasley, C. L. Frye, R. T. Gore, Jr., and P. S. Wilday, *J. Org. Chem.*, **33**, 2342 (1968). From 3a and 3b, (c) V. L. Heasley, G. E. Heasley, S. K. Taylor, and C. L. Frye, *ibid.* **35**, 2967 (1970). From 4a–c, (d) G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold, and D. E. Williamson, *ibid.*, **38**, 4109 (1973). From **5**, ref 5d and 5e, G. Heublein and M. Helbig, *Tetrahedron*, **29**, 3247 (1973).

(6) This is in contrast to a report by Bellucci[2a] who reported that the structure of the amine or their concentrations had no significant effect on product ratios.

(7) J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469 (1969).

(8) R. E. Buckles and J. P. Yuk, *J. Am. Chem. Soc.*, **75**, 5048 (1953), report a p*K* of 5.9 for Me_4NBr_3 in CH_2Cl_2 in comparison to a p*K* of 0.99 reported (ref 13c) for $PyBr_2$ in CCl_4.

(9) G. E. Heasley, V. L. Heasley, V. M. McCully, R. T. Wiegman, and R. A. Skidgel, *J. Org. Chem.*, **41**, 644 (1976).

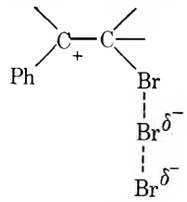
(10) The literature concerning the structures of the amine dihalogen charge transfer complexes in the solid and in solution is confusing. Hassel and Romming (ref 11a) cite X-ray crystallographic studies to support a linear amine–dihalide structure in the solid state. But, on the basis of infrared and Raman spectral data, Ginn et al. (ref 11b) conclude that $PyBr_2$ is present as a Py_2Br^+, Br_3^- salt in the solid state, as the nonionized PyBr–Br complex in nonpolar solvents, and as an equilibrium mixture of PyBr–Br with Py_2Br^+, Br_3^- in more polar solvents (e.g., CH_2Cl_2) and in the presence of excess pyridine. In a paper on the role of pyridine in the bromination of aromatic compounds, Ganesan and Jabeen (ref 11c) accept earlier conclusions by Popov and Rygg (ref 11d) that $PyBr_2$ readily gives rise to the species $PyBr^+$ and Br^-. Bellucci[2a] apparently assumes that $PyBr^+$, Br^- is the electrophilic agent in brominations with $PyBr_2$.

(11) (a) O. Hassel and C. H. R. Romming, *Q. Rev., Chem. Soc.*, **16**, 1 (1962); (b) S. G. W. Ginn, I. Haque, and J. L. Wood, *Spectrochim. Acta, Part A*, **24**, 1531 (1968); (c) R. Ganesan and Zahera J., *J. Indian Chem. Soc.*, **49**, 205 (1972); (d) A. I. Popov and R. H. Rygg, *J. Am. Chem. Soc.*, **79**, 4622 (1957).

(12) Formation constants for pyridine–halogen complexes have not been determined in methylene chloride. Formation constants ($\times 10^3$) for the BrCl complexes[13a] in CCl_4 of PyBrCl, 1.2, 2,6-LuBrCl, 1.5, and 3,5-LuBrCl, 6.8, compared to formation constants for the ICl complexes[13b] ($\times 10^5$) of PyICl, 4.8, and 2,6-LuICl, 0.89. The 2,6-Lu complexes are of lower stability than the 3,5-Lu complexes, evidently because of greater steric interactions in the former. Given the greater size of chlorine over bromine, it seems likely that 2,6-$LuBr_2$ might be less stable than $PyBr_2$. The few constants for the dibromides which have been reported[13c] ($PyBr_2$, 9.7, 3,4-$LuBr_2$, 15.4) show that the bromine complexes are much less stable than the BrCl or ICl complexes.

(13) (a) T. Surles and A. I. Popov, *Inorg. Chem.*, **8**, 2049 (1969); (b) A. I. Popov and R. H. Rygg, *J. Am. Chem. Soc.*, **79**, 4622 (1957); (c) G. G. Aloisi, G. Beggiato, and U. Mazzucato, *Trans. Faraday Soc.*, **66**, 3075 (1970).

(14) Bellucci has suggested[2a] that the reason that $PyBr_2$ and $PyHBr_3$ give similar results is because $PyHBr_3$ is converted to $PyBr_2$ but that would not be possible for Et_4NBr_3 which gives results similar to $PyBr_3$ in our study. Concerning the mechanism of bromination by Br_3^- Rolston and Yates[15] found a much less negative ρ value for bromination of a series of substituted styrenes by tribromide than for bromination by molecular bromine (−2.02 for Br_3^- vs. −4.21 for Br_2) and concluded that much less positive charge was developed on the α carbon in the transition state (we might note that the transition state proposed by these workers, see structure below, could not be consistent with our stereochemical results). Du Bois[16] has concluded that tribromide reacts by an electrophilic attack by Br_3^- in reactive alkenes compared to a nucleophilic attack by Br^- on the Br_2 charge transfer



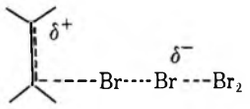
complex when the alkene is of low reactivity. On the basis of these reports, we would expect that our alkenes would probably react with Br_3^- by the $AdEC_1$ mechanism.

(15) J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1483 (1969).

(16) J. E. Dubois and X. Q. Huynh, *Tetrahedron Lett.*, 3369 (1971).

(17) G. Stork and A. F. Kreft, *J. Am. Chem. Soc.*, **99**, 3851, 3850 (1977), report considerable variation in the stereochemistry of S_N2' attack, depending upon the nature of the nucleophile and other conditions. Theoretical calculations [R. L. Yates, N. D. Epiotis, and F. Bernardi, *J. Am. Chem. Soc.*, **97**, 6615 (1975)] predict that the stereochemistry of the S_N2' reaction should be controlled by nonbonded attraction and repulsion forces. Thus the nucleophile should approach syn to the leaving group when the nucleophile is negatively charged, and the anti approach should be favored when the nucleophile is uncharged. Bordwell, *Acc. Chem. Res.*, **3**, 281 (1970), has stressed the lack of evidence for the S_N2' mechanism and has found that many reactions which appear to be S_N2' actually proceed via ion pair mechanisms.

(18) Wilson, *J. Chem. Soc., Perkin Trans. 2*, 141 (1976), has also suggested that variations in stereospecificity of bromine addition to styrenes with changes in bromine concentration could be explained by the fact that the higher order (in Br_2) mechanism would proceed directly to an open carbonium ion (structure below) whereas the unimolecular reaction would yield



a cyclic bromonium ion.

(19) Lower yields were obtained with the amine dibromides (in comparison to molecular bromine), particularly in the presence of a large excess of amine. Although we showed that this was not caused by a reaction of the amine with the dibromide products, we did not establish the reason for the loss in material balance. One possibility is that the pyridines, themselves, are brominated in competition with the alkenes.

(20) See ref 1a, p 487.

(21) A. Valette, *Ann. Chim. (Paris)*, **3**, 644 (1948).

Specificity of Cyclic Sulfides in Gas-Phase Reactions with Hydrogen Atoms

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The reactivity of cyclic sulfides toward hydrogen atoms was studied by experimental work with 3-thiolene. The reaction was carried out at 295 K under the pressures of 670 Pa and 2.1 kPa in a conventional discharge-flow apparatus. Butadiene was found to be the primary product, which reacted further with hydrogen atoms to give butene isomers. No sulfur compounds except hydrogen sulfide were detected among the reaction products. The reaction is consistent with concerted sulfur atom abstraction by hydrogen atom. Comparison with the systems involving thiirane and thiolane indicates that concerted abstraction is characteristic of the system in which the reaction product of the sulfur abstraction is highly stabilized due to π conjugation.

The gas-phase reaction of thiirane with hydrogen atoms at room temperature has been known to give ethylene and hydrogen sulfide as the main products and is noted for the complete absence of ethanethiol even under the pressure of 66 kPa.[1] The reaction was explained in terms of a unique, concerted sulfur atom abstraction by the hydrogen atom, without the intermediacy of thio radicals which may lead to ethanethiol under high-pressure conditions.

On the other hand, 1-butanethiol was the predominant product in the reaction of thiolane with hydrogen atoms under a pressure of 660 Pa over the temperature range 300–580 K.[2,3] The initial hydrogen atom addition to the sulfur atom and the subsequent C–S bond cleavage to form 4-mercapto-1-butyl radical was considered responsible for the observed product distribution.

The marked difference in the reactivity of the two cyclic sulfides toward hydrogen atoms was suggested to be due to the difference in the stabilization of the reaction products.[3] The purpose of the present study is to examine the above presumption by investigating the reaction of 3-thiolene with hydrogen atoms in the gas phase and to relate the results to other cases of cyclic sulfides including the thiophene–hydrogen atom system.

Experimental Section

The reaction was carried out in a conventional discharge-flow reactor at 295 ± 2 K under pressures of 670 ± 20 Pa and 2.1 ± 0.03 kPa. The apparatus and procedure have been described in detail in our previous papers.[3,4] 3-Thiolene was prepared by the reduction of thiophene following the method of Birch and McAllan,[5] purified by gas chromatography (GC), and identified by NMR spectra.[6]

Two samples having different purities were used in the experimental work. One sample had a purity of about 95%, the impurity consisting mainly of 2-thiolene. The other sample, obtained by a further GC purification of the above sample, had a purity of 99% and contained no trace of 2-thiolene. The former sample was used in the majority of the experimental runs. Butadiene having more than 99% purity was also subjected to the reaction with hydrogen atoms under similar conditions. In all of the experiments, the change of the conversion was attained by shifting the position of the microwave discharge cavity for generating hydrogen atoms relative to the reaction zone.

The reaction products were analyzed by GC. In particular, the identification of butenethiols was inferred from the analysis of the reaction mixture of the Birch reduction of thiophene. After extracting thiolenes and unreacted thiophene by isopentane, the remaining alkaline solution was acidified and then extracted by isopentane. The GC analysis of the isopentane extract showed, besides thiophene and the thiolenes, the presence of four substances, presumably the isomers of butenethiols.[5] The relative retention times of the four GC peaks relative to that of thiophene were 0.87, 1.16, 1.32, and 1.36, using a silicone oil column at 80 °C.

Results and Discussion

The reaction products were found to be hydrogen sulfide and hydrocarbons consisting mainly of butadiene and butene isomers. In the high conversion-range runs (>50%) with the 95% purity sample, traces of four minor components were detected. They are considered most likely to be the isomers of butenethiols in view of the agreement of their retention times on GC with those observed for the four substances in the isopentane extract mentioned above. Since these products were not at all detected when the purer sample was used, it is clear that they were the products from 2-thiolene present as impurity. Therefore, they were not taken into consideration in the following discussion.

The change of the hydrocarbon selectivities with the conversion is illustrated in Figure 1. The products can be divided into three groups: butadiene, butene isomers, and the rest. Butadiene is apparently the primary product, from which result the hydrogenation products butene isomers. The third group products are considered derived from the reactions of the butene isomers with hydrogen atoms.

The distribution of the hydrocarbon products can be compared with that which arises from the reaction of butadiene with hydrogen atoms under similar conditions. The product distribution in the butadiene–H system was found to be more diverse than in the case with 3-thiolene–H. 3-Methyl-1-butene and *trans*- and *cis*-2-pentenes were among C_5–C_8 products which were not found in the 3-thiolene–H reaction products. However, the sum of the yield of these compounds never exceeded 15% of the sum of the yield of the reaction products. The comparison with the 3-thiolene–H system was therefore based on the products excluding the above C_5–C_8 products.

Since in the butadiene–H system the conversion corresponding to that for the 3-thiolene–H system cannot be defined, the following procedure was taken to effect the comparison. First, it is assumed that a total product mixture of a butadiene–H run represents the hydrocarbon product mixture of a 3-thiolene–H run. Secondly, the value of the conversion which gives the mole percent of butadiene equal to that found for the above mixture is read from the smoothed conversion–selectivity curve for butadiene in Figure 1. Finally, the selectivity of each of the hydrocarbons in the mixture is plotted at the particular conversion. The results are illustrated in Figure 2. The smoothed curves are the duplicates of those drawn in Figure 1.

It is clearly shown that the product distribution pattern of the butadiene–H reaction is identical with the hydrocarbon product pattern of the 3-thiolene–H reaction. This fact suggests that butadiene is formed exclusively in the initial reaction much faster than in the subsequent reactions, in which butadiene is consumed gradually by the remaining hydrogen atoms.

The reaction which leads to the undisturbed initial formation of butadiene is consistent with the concerted sulfur atom abstraction by the hydrogen atom via the transition state

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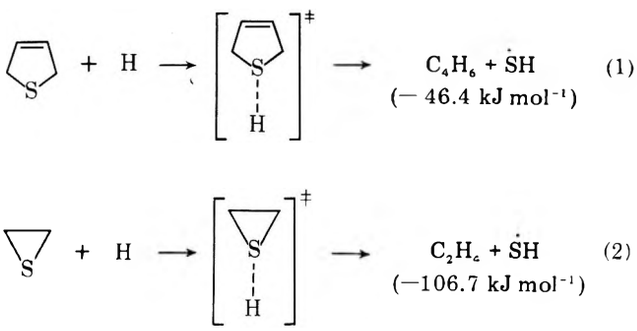
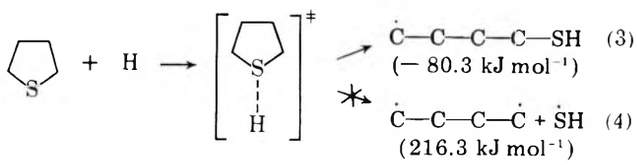
shown in the following scheme. This reaction scheme is very similar to that proposed for the thiirane–H system[1,7] in which



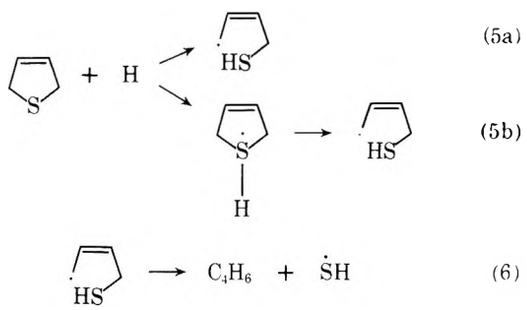
the divalent sulfur atom at the bridgehead position is abstracted by a monovalent radical. It is readily apparent in these examples that the hydrocarbon products are highly stabilized by π conjugation.

On the other hand, similar sulfur atom abstraction from thiolane is considered improbable, since the hypothetical product radical Ċ–C–C–C–Ċ lacks the stability that is quite significant in 3-thiolene and thiirane cases. The formation of the mercaptobutyl radical by the cleavage of the C–S bond is instead the most probable path out of the transition state, as shown below.

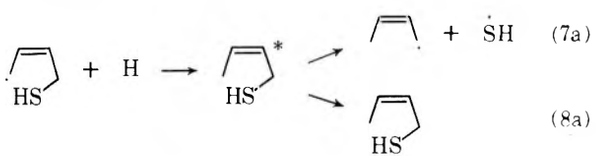


Thus, concerted sulfur atom abstraction from the cyclic sulfides by a monovalent radical may be characteristic to the systems in which the product hydrocarbon is stabilized by π conjugation; otherwise C–S bond dissociation will be the primary step.

An alternative mechanism which seems also consistent with the experimental results may be considered. This involves the formation of the mercaptobutenyl radical (either in a direct displacement (5a) or in the fragmentation of the intermediate with the shell-expanded sulfur atom (5b)) followed by the elimination of the sulfhydryl radical (6).



The mercaptobutenyl radical may further react with hydrogen atom to form chemically activated butenethiols, which may either decompose to give butenyl and sulfhydryl radicals (7a, 7b) or collisionally stabilize to butenethiols (8a, 8b), depending on the reaction conditions.



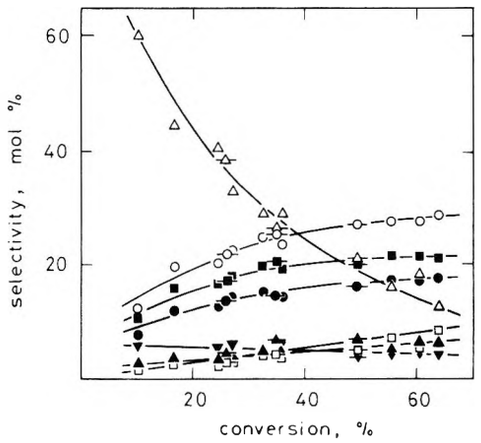


Figure 1. Conversion–selectivity relationship, 3-thiolene–H system, 295 K, 670 Pa: △, butadiene; ○, *trans*-2-butene; ○, *cis*-2-butene: ■, 1-butene; ▲, propylene; ▼, ethylene; □, *n*-butane. Symbols with the horizontal bars are the results of the 99% purity sample. The rest is based on the 95% purity sample.

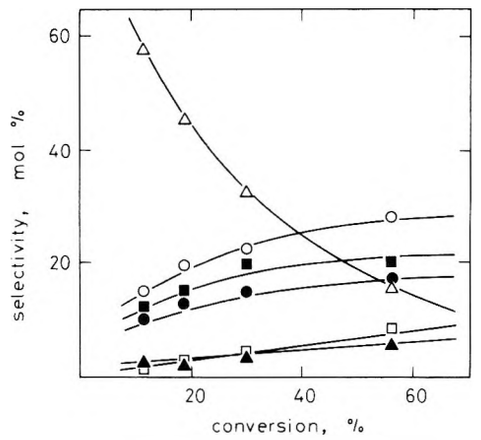
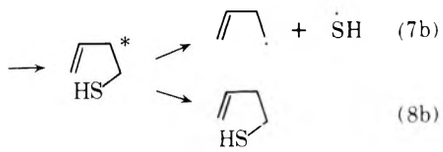


Figure 2. Conversion–selectivity relationship, butadiene–H system, 295 K, 670 Pa. For legends, see Figure 1. Results for ethylene are not shown due to its negligible formation.



(The symbol * represents vibrational excitation.)

It has been shown, however, that under the present experimental conditions the isomers of butenethiol were not observed among the reaction products.[8] Therefore, it is considered that this two-step mechanism cannot adequately explain the experimental findings.

This aspect can further be substantiated by the results of the experiment carried out at 295 K under a pressure of 2.1 kPa where an enhanced stabilization should occur. In a typical run using the 99% purity sample with a conversion of 16%, the selectivity of the reaction products in mole percent was the following: butadiene 51%, *cis*-2-butene 11%, *trans*-2-butene 17%, 1-butene 16%, *n*-butane 1%, propylene 2%, and ethylene 3%. Formation of other products, in particular those assumed to be butenethiols, was hardly noticeable.

A somewhat similar observation was noted in the case of the reaction of thiirane with hydrogen atoms,[1] as mentioned earlier. It was stated that under a pressure of about 66 kPa, ethanethiol, the possible stabilization product, was shown to be demonstratively absent.

It is interesting to examine the relative yields of butene

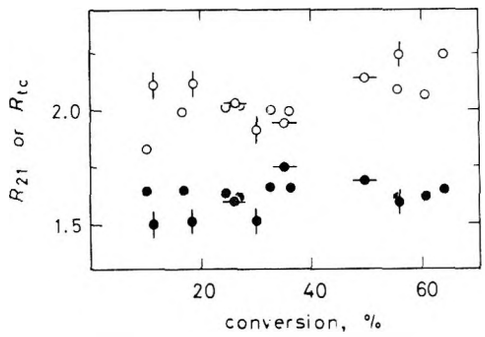


Figure 3. Conversion vs. R_{21} or R_{tc}, 295 K, 670 Pa: ○, R_{21}; ●, R_{tc}, 3-thiolene–H system. Symbols with the horizontal bars are the results of the 99% purity sample. Symbols with vertical bars are for butadiene–H system.

isomers in both 3-thiolene–H and butadiene–H systems. The reatios R_{21} = (2-butenes)/(1-butene) and R_{tc} = (*trans*-2-butene)/(*cis*-2-butene) are calculated and plotted against the conversion. The results are shown in Figure 3. The results of the 3-thiolene–H system are found to be the same as those for the butadiene–H system. Both R_{21} and R_{tc} are independent of the conversion. For the 3-thiolene case, the average values are calculated to be $R_{21} = 2.07 \pm 0.05$ (standard deviation) and $R_{tc} = 1.65 \pm 0.01$. These ratios are different from the equilibrium values $R_{21} = 41$ and $R_{tc} = 3.2$ at 300 K.

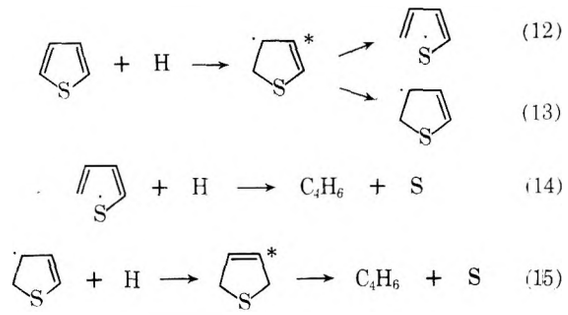
The comparable formation of isomers of 2-butene and 1-butene can be explained by the competitive hydrogen atom addition to the different carbon atoms of 1-buten-3-yl radical, formed by the predominantly terminal addition of the hydrogen atom to butadiene,[9] as shown below.

$$C{=}C{-}C{=}C + H \longrightarrow C{=}C{-}\dot{C}{-}C \;(C\cdots C\cdots C{-}C) \quad (9)$$

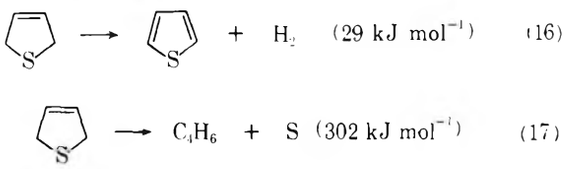
$$C{=}C{-}\dot{C}{-}C + H \rightarrow \begin{cases} C{-}C{=}C{-}C & (10) \\ C{=}C{-}C{-}C & (11) \end{cases}$$

The restricted rotation about the central C–C bond of the radical due to the allylic stabilization[10] may account for the formation of the isomers of 2-butene in the moderately different ratio from the equilibrium.

The ratios R_{21} and R_{tc} for the thiophene–H system are found to be 1.51 ± 0.01 and 1.69 ± 0.20, respectively, for the conversion range of 2.5–18.4% at 300 K.[11] These values are very close to those observed for the 3-thiolene–H and butadiene–H systems, although 1-butene formation seems slightly more favored in the thiophene–H system. In this system, the formation of butadiene was explained by the decomposition of the unsaturated thio radical formed in step (12) upon the attack of a hydrogen atom, step (14). However, the results obtained for the 3-thiolene–H system, together with the fact that no sulfur compounds except hydrogen sulfide were found in the reaction products for the thiophene–H system, suggest an alternative process leading to the formation of butadiene. If the stabilized 2-thiolen-4-yl radical is formed in step (13), the chemically activated 3-thiolene is expected to be formed by the addition of a hydrogen atom to the thiolenyl radical. The activated 3-thiolene is then assumed to decompose completely to yield butadiene and the sulfur atom, step (15).



The last step (15) may be compared with the results of the pyrolysis of 3-thiolene in the gas phase.[12] Homogeneous elimination of hydrogen to form thiophene took place in the temperature range 610–690 K, step (16). It was noted, however, that hydrogen sulfide amounting to some 30% of the thiophene, together with a polymer material, was produced in addition to the equimolar mixture of hydrogen and thiophene. It was noted also that the hydrogen sulfide was possibly produced during the polymer formation. It can be speculated that the hydrogen sulfide was formed by the consequence of reaction 17. The endothermicity of reaction 17 of about 300



kJ mol^{-1} can be expected to be overcome once the reaction enters into some radical chain reactions in which the sulfur atom initiates the free radical chain leading to the accumulation of the polymer materials.

Acknowledgment. We would like to thank Dr. Takayuki Ono of the Department of Applied Chemistry for carrying out the Birch reduction of thiophene.

Registry No.—3-Thiolene, 1708-32-3.

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Transfer Hydrogenation and Transfer Hydrogenolysis. 16. Dehydrogenation by Tetracyanoethylene

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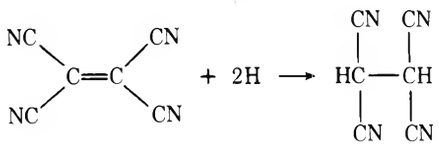
Several benzyl-type alcohols and hydroaromatic compounds were dehydrogenated by tetracyanoethylene (TCNE). The hydrogen transfer from 1-phenylpropanol was studied in detail. The yield of propiophenone increased when solvents which seem to increase the concentration of the complex between TCNE and the alcohol or to stabilize ionic species were used. Initial rates of the reaction were proportional to the concentration of the hydrogen donor and the hydrogen acceptor. In the reaction of several para- or meta-substituted 1-phenylpropanols in dioxane at 100 °C, −3.13 was obtained as a value of the reaction constant. Relative rates of the reaction of PhCH(OH)Et, PhCH(OD)Et, PhCD(OH)Et, and PhCD(OD)Et were 2.8, 2.5, 1.1, and 1, respectively. This means that the transfer of the hydrogen attached to the α position of the alcohol is the rate-determining step. Discussions about the mechanism of this hydrogen-transfer reaction are given.

The thermal hydrogen transfer from some types of organic compounds to high-potential quinones is well known.[1] However, reports of hydrogen transfer to olefins are relatively scarce.[2] It has been reported that 1,4-dihydrobenzenes[2a,b] and 9(11)-dehydroergosteryl acetate[2c] are dehydrogenated by tetracyanoethylene (TCNE). However, so far as we know, the thermal hydrogen transfer from alcohols to olefins has not been reported.

During the course of the investigation of catalytic hydrogen transfer from organic compounds to olefins[3] and a quinone,[4] we found that TCNE dehydrogenates several organic compounds without catalysts. Since we were interested in the transfer of hydrogen atoms from the 1,2 positions of hydrogen donors to the 1,2 positions of hydrogen acceptors, as described later, and the preparation of derivatives of benzyl-type alcohols seemed to be relatively easy, we studied the hydrogen transfer from benzyl-type alcohols to TCNE in detail.

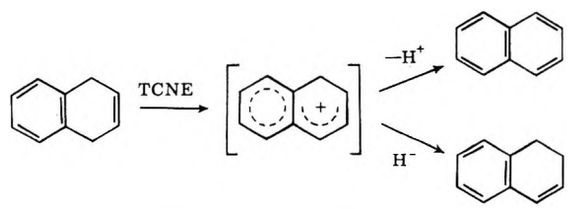
Results and Discussion

Hydrogen-Donating Ability. At first the susceptibility of organic compounds to dehydrogenation by TCNE was investigated under the following reaction conditons: a hydrogen donor (0.2 M) and TCNE (0.2 M) were heated at 60, 100, and 140 °C for 3 h in dioxane, which has been used as a solvent in most cases in dehydrogenation by dichlorodicyanobenzoquinone (DDQ).[1b] In addition to the dehydrogenation products anticipated, a white crystalline compound was isolated from the reaction mixtures in some cases and identified as 1,1,2,2-tetracyanoethane by comparison of melting point and IR spectrum with those of an authentic sample.[5] This fact shows that the following reaction proceeded.



It has been reported that TCNE undergoes substitution reactions with alcohols,[6] amines,[6,7] and aromatic compounds,[8] addition reactions with ketones,[9] and Diels–Alder reactions with dienes, including anthracene.[2a] Therefore, to obtain dehydrogenation products in good yields, the rates of the dehydrogenation reaction must be higher than those of these side reactions. If the hydrogen donors or the dehydrogenation products that form undergo side reactions, the total amount of the donors that survive and the dehydrogenation products that form becomes smaller than the amount of the donors charged. Accordingly, not only was the amount of the dehydrogenation products measured, but also the amount of the hydrogen donors that remains unreacted.

As hydrogen donors, several alcohols and hydroaromatic compounds were examined, and the results are summarized in Table I. As previously anticipated, alcohols and hydroaromatic compounds were dehydrogenated to give the corresponding carbonyl and aromatic compounds, respectively. In the reactions at 60 °C, cinnamic alcohol, 1,4-dihydronaphthalene, and 2,5-dihydrofuran were dehydrogenated considerably. In the reactions at 100 °C, the yield of dehydrogenation products decreased in the following order: cinnamic alcohol > 1,4-dihydronaphthalene > 2,5-dihydrofuran > 1,2,3,4-tetrahydroquinoline > 1-phenylethanol > 9,10-dihydroanthracene > 1-phenylpropanol > benzhydrol > benzyl alcohol > 1-phenyl-2-methylpropanol > 1,2-dihydronaphthalene. Side reactions were intensive in the reactions of benzhydrol, benzyl alcohol, and 1,2,3,4-tetrahydroquinoline and considerable in the reactions of 1-phenylethanol, cinnamic alcohol, 2,5-dihydrofuran, 1,4-dihydronaphthalene, and 9,10-dihydroanthracene. In the reactions at 140 °C, the hydrogen-giving ability decreased in the following order: 2,5-dihydrofuran > cinnamic alcohol > 1,4-dihydronaphthalene > 9,10-dihydroanthracene > 1,2,3,4-tetrahydroquinoline > 1-phenylpropanol > 1-phenylethanol > 2-methyl-1-phenylpropanol > benzhydrol > 1,2-dihydronaphthalene > benzyl alcohol. In the reaction of 1,4-dihydronaphthalene, isomerization to 1,2-dihydronaphthalene occurred considerably. This



fact suggests that a carbonium ion is formed in the course of the dehydrogenation.

When 1,2-dihydro-1,1-dimethylnaphthalene was used as a hydrogen donor, rearrangement of a methyl group occurred and 1,2-dimethylnaphthalene was formed, although the yield was low. This fact also suggests that an electron deficient species was formed by the hydride abstraction at the 2 position of the hydrogen donor.

Indoline, 1-propanol, 2-propanol, and tetraline did not give the dehydrogenation products expected in the reactions at 100 and 140 °C.

Furthermore, we tried dehydrogenation by benzylidene malononitrile derivatives and fumaronitrile in reactions at 120

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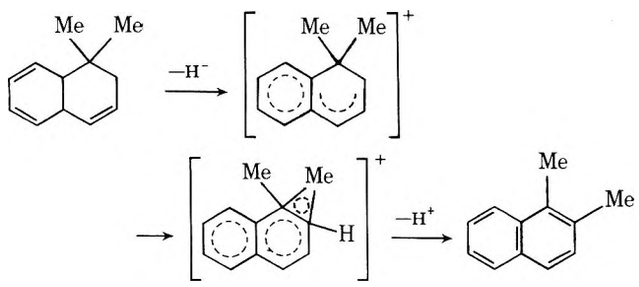
Table I. Dehydrogenation by TCNE [a,d]

Hydrogen donor	Registry no.	Reaction temp, °C	Yield of dehydrogenation product, %	Recovery of hydrogen donor, %
Benzyl alcohol	100-51-6	60	1	50
		100	7	52
		140	20	38
1-Phenylethanol	98-85-1	60	3	96
		100	24	64
		140	30	19
1-Phenylpropanol		60	2	95
		100	17	76
		140	34	27
2-Methyl-1-phenylpropanol	611-69-8	60	1	91
		100	6	89
		140	29	51
Benzhydrol	91-01-0	60	2	45
		100	13	26
		140	28	1
Cinnamic alcohol	104-54-1	60	24	34
		100	68	9
		140	70	0
2,5-Dihydrofuran	1708-29-8	60	7	71
		100	46	34
		140	82	4
1,4-Dihydronaphthalene	612-17-9	60	18	75[b]
		100	60	24[b]
		140	65	6[b]
1,2-Dihydronaphthalene	447-53-0	100	6	96
		140	25	67
1,2-Dihydro-1,1-dimethylnaphthalene	2733-79-1	140	5[c]	90
9,10-Dihydroanthracene	613-31-0	60	2	88
		100	24	59
		140	45	49
1,2,3,4-Tetrahydroquinoline	635-46-1	100	30	23
		140	40	15

[a] A hydrogen donor (0.2 M) and TCNE (0.2 M) were heated in dioxane for 3 h. [b] Intensive isomerization to 1,2-dihydronaphthalene was observed. [c] The dehydrogenation product was 1,2-dimethylnaphthalene. [d] Registry no.: TCNE, 670-54-2.



°C for 18 h in dioxane. When *m*-nitrobenzylidene malononitrile was used as a hydrogen acceptor, tetrahydroquinoline and indoline gave quinoline and indole in yields of 19 and 16% and were recovered in 72 and 43% yields, respectively. Cinnamic alcohol and 2,5-dihydrofuran formed trace amounts of cinnamaldehyde and furan, but 1-phenylpropanol and 1,2- and 1,4-dihydronaphthalenes did not undergo the dehydrogenation reaction. In the reaction of benzylidene malononitrile, indoline gave a trace (ca. 2%) of indole, but tetrahydroquinoline did not form quinoline. Both indoline and tetrahydroquinoline were not dehydrogenated by *p*-methoxybenzylidene malononitrile under the reaction conditions. These results show that electron-withdrawing substituents attached to olefinic bonds promote the dehydrogenation reaction and the hydrogen-donating power of hydroaromatic compounds containing a nitrogen atom is strong. Fumaronitrile did not dehydrogenate even the amines described above.

As a hydrogen donor, 1-phenylpropanol and its derivatives were used in any experiment described hereafter because (1) we were interested in the hydrogen transfer from alcohols from a mechanistic viewpoint, (2) the alcohol showed a low tendency to cause side reactions and a relatively high hydrogen-giving ability, and (3) the preparation of its derivatives seemed to be easy.

Reaction Solvents. The effect of solvents was investigated to find suitable solvents and to discuss the mechanisms of the dehydrogenation reaction. Solvents that dissolved TCNE well and did not cause observable side reactions were chosen, and the results are summarized in Table II. The yield of propiophenone decreased in the following order: acetic acid > propionic acid > tetrahydrofuran > chloroform > ethyl acetate > dioxane > dichloromethane > chlorobenzene > anisole > phenetole > benzene.

Based on analogy to the dehydrogenation of hydroaromatic compounds by quinones[1] and on the fact that TCNE forms charge-transfer (CT) complexes with aromatics[10] and ethers,[10a,11] it is inferred that dehydrogenation by TCNE also occurs via the formation of CT complexes. Therefore, we speculated that the influence of solvents may be interpreted by the stabilization of the CT complexes and/or other active species, including the transition state of the reaction, by solvation. At first, we tried to identify the absorption band belonging to the TCNE/1-phenylpropanol complex in various solvents, but the bands could not be identified clearly. When toluene was used instead of the alcohol, the band due to the TCNE/toluene complex appeared at 406 nm[10a] in dichloromethane, but it overlapped with the peaks attributable to the CT complexes between TCNE and some solvents, including dioxane and tetrahydrofuran. Eventually, the relative amount of the TCNE/anisole complex was measured to estimate roughly the relative amount of the TCNE/1-phenylpropanol complex in the designated solvents. Along with the wavelength at the maximum absorption (λ_{CT}), the absorbance (log (I_0/I)) is shown in Table II. The absorbance measured showed close relationship with λ_{CT}, and this fact indicates that the ease of formation of the CT complex is influenced by solvation.[12] In the reactions using solvents of similar structure, considerable correlation was observed between the yield of propiophenone and the values of the absorbance. This result suggests that the dehydrogenation reaction proceeds via the formation of CT complexes which lie before the rate-determining step of the reaction. However, the absorbance was not so closely related with the yield of the ketone in reactions in solvents of unlike structure. From this result it is assumed that solvation of other active species, perhaps the transition state of the rate-limiting step, is more important than that of the CT complex, which seems to be relatively stable.

Then we tried to correlate the yield of propiophenone to the dielectric constants of the solvents (ϵ) and the transition energy for the CT bands of pyridinium *N*-phenolbetaine (E_T) and 1-ethyl-4-carbomethoxypyridinium iodide (Z) in a given solvent.[12] These parameters are regarded as quantitative measures of ionizing power.[12] The yield of ketone seems to be explained by ϵ, E_T, and Z in a rough sense, except for the reaction in dioxane where the yield was too high and in dichloromethane where the yield was too low (Table II). The result that this hydrogen-transfer reaction proceeded more rapidly in more polar solvents suggests that the transition state of the rate-determining step is considerably charge separated. On the other hand, it is presumed that the amount of the transferred charge of the TCNE/1-phenylpropanol complex is not so large because the yield of the ketone hardly correlated with the values of ϵ, E_T, and Z of the solvents used. This presumption may be supported by the report that very little

Table II. Effect of Solvents [a]

Solvent	Yield of ketone, %	Recovery of alcohol, %	λ_{CT},[b] nm	log (I_0/I)[c]	ϵ[d]	E_T,[e] kcal mol^{-1}	Z,[f] kcal mol^{-1}
Acetic acid	28	70	480	0.32	6.2	51.9	79.2
Propionic acid	21	64	486	0.38	3.4		
Tetrahydrofuran	21	59	470	0.19	7.6	37.4	
Chloroform	18	82	512	1.2	4.8	39.1	63.2
Ethyl acetate	18	65	470	0.21	6.0	38.1	
Dioxane	14	81	460	0.15	2.2	36.0	
Dichloromethane	13	75	507	0.77	9.1	41.1	64.2
Chlorobenzene	12	76	510	1.0	5.6	37.5	
Anisole	10	83	*g*	*g*	4.3	37.2	
Phenetole	8	77	*g*	*g*	4.2		58.9
Benzene	7	90	490	0.61	2.3	34.5	54.0

[a] 1-Phenylpropanol (0.2 M) and TCNE (0.2 M) were heated at 100 °C for 2 h. [b] Wavelength of the absorption maxima of the band owing to the CT complex between TCNE (2 mM) and anisole in anisole/solvent (1:9 in volume) mixture. [c] Absorbance of the band described above. [d] Dielectric constant. [e] Molar transition energy of pyridinium *N*-phenolbetaine in the designated solvent.[12] [f] Same as E_T, except for the use of 1-ethyl-4-carbomethoxypyridinium iodide as the test substance.[12] [g] The absorption of the CT complex was covered by that of the solvent.

charge transfer is involved in stabilizing TCNE molecular compounds.[10b]

The basicity of solvents seems to be scarcely correlated with the yield of ketone.

Strongly polar solvents such as *N,N*-dimethylacetamide, dimethyl sulfoxide, sulfolane, acetonitrile, acetone, trifluoroacetic acid, methanol, and water caused extensive side reactions, and the total amount of the propiophenone that formed and the 1-phenylpropanol that survived diminished greatly in most cases. Since all of the protonic solvents except for acetic acid and propionic acid caused side reactions, we suspected the stability of TCNE in the presence of acids. However, it was confirmed by a spectroscopic study that the amount of TCNE did not decrease when TCNE (0.1 M) and acetic acid (0.2 M) were heated at 100 °C for 1 h in dioxane.[13]

Nonpolar solvents such as *n*-octane, decaline, diethyl ether, and diisopropyl ether did not dissolve TCNE completely even at 100 °C.

Effect of Additives. The effect of additives was examined in a reaction in which 1-phenylpropanol (0.2 M), TCNE (0.2 M), and an additive (0.2 M) were heated at 100 °C for 2 h in dioxane, and the results are shown in Table III.

In spite of the report that dimethyl sulfoxide and *N,N*-dimethylacetamide react with TCNE to give anion radical species,[14] the addition of them raised the yield of propiophenone, though it caused observable side reactions. Other polar additives such as sulfolane, acetonitrile, and methanol showed no promoting effect. It has been reported that the dehydrogenation of 1,4-dihydronaphthalene by quinones is catalyzed by acids.[15] However, in our system the addition of acids showed no promoting effect.

Pyrocatechol and hydroquinone, which are inhibitors of radical reactions, did not retard the dehydrogenation reaction, and benzoylperoxide and α,α'-azobis(isobutyronitrile) (0.02 M), which are initiators of radical reactions, did not promote the reaction. This result makes it unlikely that the hydrogen-transfer reaction proceeds via a radical process,[15,16] although the result does not necessarily deny the existence of radical intermediates.

By the addition of strong bases, such as sodium acetate, pyridine, and triethylamine, the yield of ketone became negligible.

Measurement of Reaction Rates. In Figure 1 an example of the yield of propiophenone against reaction time is shown. At the initial stage of the reaction the yield of ketone was proportional to time up to about 20% in this case. The initial rate of this hydrogen-transfer reaction was derived from the linear part of the plot.

Table III. Effect of Additives [a]

Additive	Yield of ketone, %	Recovery of alcohol, %
Dimethyl sulfoxide	21	47
N,N-Dimethylacetamide	17	48
Sulfolane	14	80
Acetonitrile	13	80
Methanol	13	84
Acetic acid	14	80
Trifluoroacetic acid	13	76
Dichloroacetic acid	12	80
Pyrocatechol	14	81
Hydroquinone	12	63
Benzoyl peroxide[b]	12	70
α,α'-Azobis-(isobutyronitrile)[b]	11	68
Pyridine	1	68
Sodium acetate	1	85
Triethylamine	0	70
None	14	81

[a] 1-Phenylpropanol (0.2 M), TCNE (0.2 M), and an additive (0.2 M) were heated at 100 °C for 2 h in dioxane. [b] The amount of this additive was 0.02 M.

In most of the dehydrogenations by quinones, second-order kinetics has been reported.[1] In the dehydrogenation by TCNE, also, the initial rate was found to be proportional to the concentration of 1-phenylpropanol and TCNE, as shown in Figure 2. Furthermore, the fact that the proportionality was observed over a wide range of concentration of the reactants suggests that if this reaction proceeds via the formation of a complex between TCNE and the alcohol, the concentration of the complex is not to high because formation of the complex in high concentration would require deviation from the linearity shown in the plots in Figure 2.

As described previously, the rate seems to be proportional to the concentration of the CT complex in similar solvents. So the reaction scheme and rate may be expressed as follows. In these expressions, HD, K, k, and k_{obsd} represent 1-phenylpropanol, the equilibrium constant in the formation of the CT complex, the rate constant of the rate-determining step, and the observed second-order rate constant, respectively.

$$\text{TCNE} + \text{HD} \overset{K}{\rightleftarrows} [\text{complex}] \xrightarrow{k} \text{products}$$

$$\text{rate} = k_{obsd}[\text{TCNE}][\text{HD}] = k[\text{complex}] = kK[\text{TCNE}][\text{HD}]$$

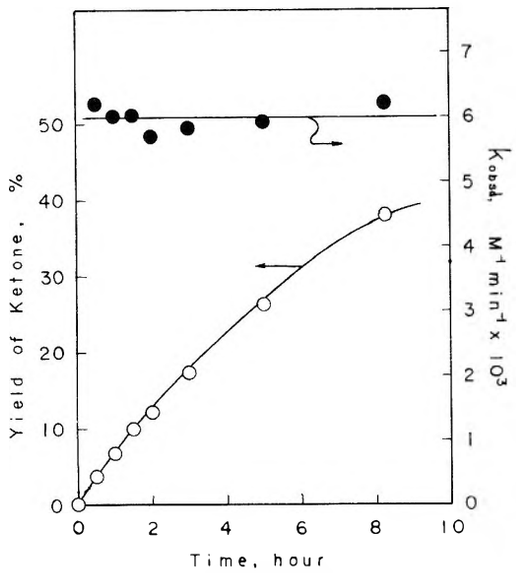


Figure 1. Plots of the yield of ketone (○) and rate constant (●) vs. reaction time. TCNE (0.2 M) and 1-phenylpropanol (0.2 M) were heated at 100 °C in dioxane.

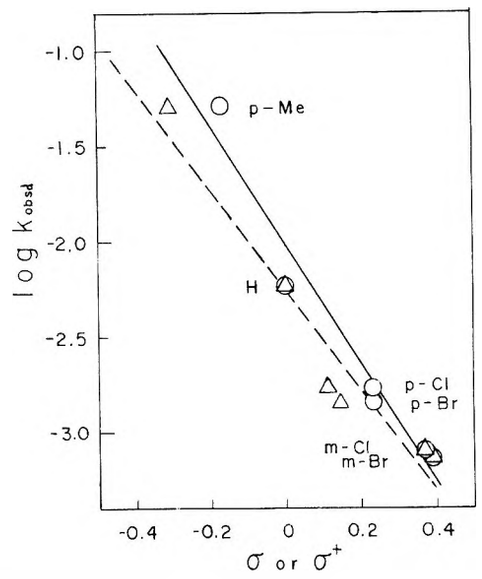


Figure 3. Plots of log k_{obsd} vs. σ (– ○ –) and σ^+ (- - - △ - - -). TCNE (0.2 M) and a para- or meta- substituted 1-phenylpropanol (0.2 M) were heated in dioxane.

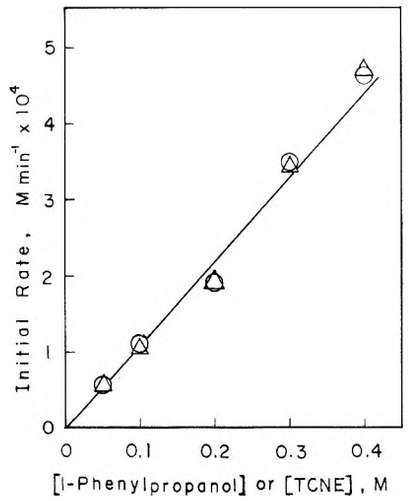


Figure 2. Plots of initial rate vs. the concentration of 1-phenylpropanol (○) and tetracyanoethylene (△); the concentration of the other reactant was 0.2 M, the temperature was 100 °C, and the solvent was dioxane.

The values of the observed second-order rate constants were found to be almost constant up to the conversion of about 40%, as shown in Figure 1. This result indicates that side reactions are not so intensive in the initial stage of the dehydrogenation reaction.

The observed second-order rate constants were measured in dioxane at temperatures ranging from 80 to 120 °C, and a plot of the logarithm of the rate constants against the reciprocal of the reaction temperatures (K) was found to show a good linear relationship, indicating that the kinetics of the system are not to complicated. From the plot, 17.8 kcal mol^{-1}, 17.1 kcal mol^{-1}, and −31.7 eu were obtained as values for the Arrhenius energy of activation (E_a), the activation enthalpy (ΔH^*), and the activation entropy (ΔS^*) at 100 °C. The values of E_a and ΔS^* at 100 °C in the hydrogen transfer from 1,4-dihydronaphthalene to benzoquinone in phenetole, 18.9 kcal mol^{-1} and −28.2 eu, have been reported as the values of E_a and ΔS^* at 100 °C.[15] The similarity of the values of the corresponding kinetic parameters suggests a similarity of reaction mechanism.

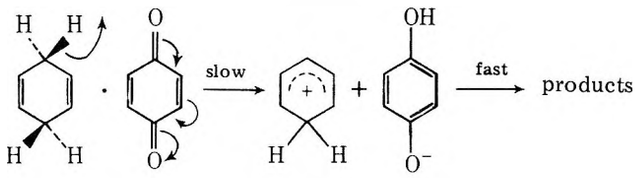
Effect of Substituents. In a review Jackman has reported that in the dehydrogenation of a series of 6- and 7-substituted 1,2-dihydronaphthalenes by a quinone, the rates correlate with the Hammett σ, or better still the σ^+, values of the substituents, and the observation that $\rho = -2.7$ is indicative of a fairly high sensitivity toward changes in substitution.[1a] Hanstein et al. have reported that the charge-transfer frequencies for complexes of TCNE with substituted benzenes correlate with σ^+ and treated the data in connection with the ability of substituents to stabilize carbonium ions.[17]

In order to discuss the electronic effect in the dehydrogenation by TCNE, *p*-methoxy, *p*-methyl, *p*-chloro, *p*-bromo, *m*-chloro, and *m*-bromo derivatives of 1-phenylpropanol were synthesized, and the second-order rate constants of the reaction of TCNE with them were measured at 100 °C in dioxane. However, in the reaction of the *p*-methoxy derivative, a reliable rate constant was not obtained because side reactions were remarkable.

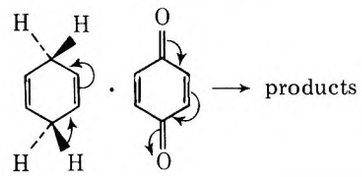
Using the least-squares method, the logarithm of the second-order rate constants was correlated to σ to give a reaction constant of ρ of −3.13 and a correlation coefficient r of −0.976, while correlating it to σ^+ gave $\rho = -2.63$ and $r = -0.968$, as shown in Figure 3. The fairly large negative ρ values seem to show that the transition state of the rate-determining step of this reaction is much more charge separated than the species which exist before the rate-limiting step. Furthermore, these ρ values are comparable to the value reported by Jackman.[1a] The resemblance of the ρ values suggests that the reaction mechanisms of the dehydrogenation of alcohols by TCNE and that of 1,2-dihydronaphthalenes by a quinone are mutually similar.

Kinetic Isotope Effect. Müllar has reported that the rate of hydrogen transfer from 1,4-cyclohexadiene to DDQ is ten times faster than that from 1,4-cyclohexadiene-d_8 and assumed, based on the enormously large kinetic isotope effect, that cleavage of the C_1–H and C_4–H bonds occurs simultaneously in the rate-determining step.[18] Burstein and Ringold have also found that the dehydrogenation of 3α-deuterio-Δ^4-3-hydroxy steroids by DDQ was subject to a primary deuterium isotope effect (ca. fivefold).[19] However, Hashish and Hoodless obtained the result that no primary isotope effect was observed in the dehydrogenation of 1,4-dihydronaphthalene (RH_2) by tetrachlorobenzoquinone (Q) in phenetole and concluded that the rate-determining step of the reaction is not the hydrogen-transfer steps (3 and 4) but

Scheme I



Scheme II



the electron-transfer step between the charge-transfer complexes (2).[28]

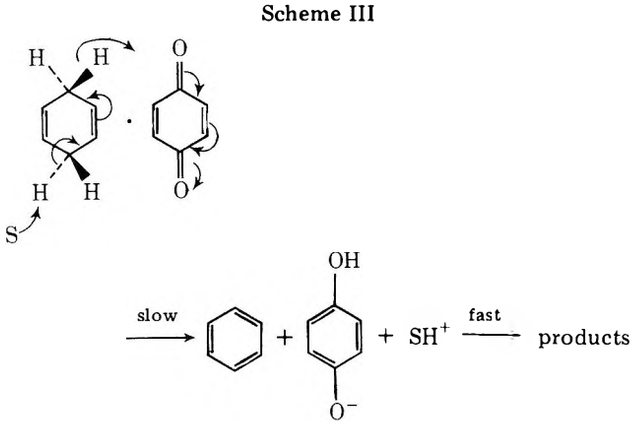
$$RH_2 + Q \overset{1}{\rightleftarrows} [RH_2 \cdot Q] \overset{2}{\rightleftarrows} [RH_2^+ \cdot Q^-] \overset{3}{\rightarrow} RH^+$$

$$+ QH^- \overset{4}{\dashrightarrow} R + QH_2$$

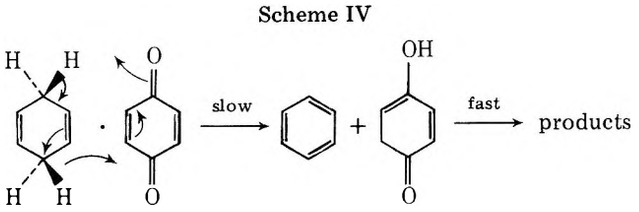
We prepared PhCD(OH)Et (CD, OH), PhCH(OD)Et (CH, OD), and PhCD(OD)Et (CD, OD), and the rates of reaction of them and PhCH(OH)Et (CH, OH) with TCNE were measured in dioxane at 100 °C. The ratios of the rates are summarized as follows: rate (CH, OH):(CD, OH) = 2.5:1; rate (CH, OD):(CD, OD) = 2.5:1; rate (CH, OH):(CH, OD) = 1.1:1; and rate (CD, OH):(CD, OD) = 1.1:1. It does not seem to be too unreasonable to consider that a primary isotope effect was observed in the transfer of the hydrogen attached to the α carbon of the alcohol while only a secondary isotope effect was observed in the transfer of the hydrogen atom of the hydroxyl group. This result suggests that cleavage of the C_α–H bond is of primary importance in the rate-determining step but that cleavage of the O–H bond is only of secondary importance or is not involved in the step.

Mechanistic Discussion. As for the dehydrogenation of 1,4-cyclohexadienes by quinones, four reaction mechanisms, as depicted below, have been proposed. Braude et al. came to the conclusion that the hydrogen transfer reaction consists of a rate-limiting hydride anion transfer from the hydrogen

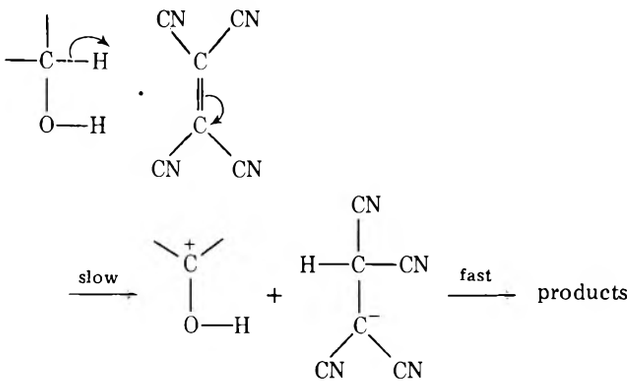
Scheme III



Scheme IV



Scheme V



donors to the hydrogen acceptors, leading to a delocalized carbonium ion which loses a proton in a subsequent rapid step (Scheme I).[1a] They considered the possibility of forming benzenes in a single-step reaction (Scheme II) in which two cis hydrogen atoms are transferred to the oxygen atoms of the quinones (1,6-addition), but they rejected the concerted cyclic mechanism on the basis of the observation that the dehydrogenation rates for 1,2- and 1,4-dihydronaphthalenes by 1,2- and 1,4-quinones are insensitive to the internuclear distances of the hydrogen atoms undergoing transfer and the two quinone oxygen atoms.[20] Furthermore, they considered a mechanism involving solvents (S) as proton acceptors (Scheme III), but they rejected it also when they found that the rate of the dehydrogenation shows little dependence on the basicity of the solvents.[21] Stoos and Rocek found that the dehydrogenation with DDQ of 1,4-cyclohexadienes, which can form aromatic hydrocarbons in a one-step dehydrogenation, is about three orders of magnitude faster than that for 1,4-dienes, which cannot form aromatics in a single-step reaction, and concluded that the dehydrogenation must involve the simultaneous breaking of two carbon–hydrogen bonds.[22] They preferred 1,4-reduction of the quinone (Scheme IV), which is symmetry allowed, to 1,6-addition of hydrogen atoms to the quinone (Scheme II), which is symmetry forbidden. Later, Müller supported most strongly the concerted mechanism involving solvents (Scheme III) by comparing the rates of dehydrogenation of various hydrogen donors by DDQ.[18]

By analogy to the dehydrogenation of dihydrobenzenes by quinones, the following three reaction schemes may be considered for hydrogen transfer from alcohols to TCNE. Schemes V and VII correspond to Schemes I and III, respectively, and Scheme VI corresponds to Schemes II and IV. Scheme V, which is two-step ionic process, seems to be most reasonable because (1) a highly charge-separated transition state was required by the effect of solvents and the fairly large negative values of ρ, (2) a primary istope effect was observed in the transfer of the hydrogen atom attached to the α carbon of 1-phenylpropanol, and (3) no phenomenon which conflicts with this scheme was observed. In this scheme the possibility of involvement of solvent in the non-rate-determining second step cannot be denied. In Scheme VI, which is a one-step cyclic process, the transfer of hydrogen is symmetry allowed because the two hydrogen atoms attached at the adjacent position of the alcohol transfer to the adjacent carbon atoms of TCNE. However, this concerted scheme does not seem to be to con-

Scheme VI

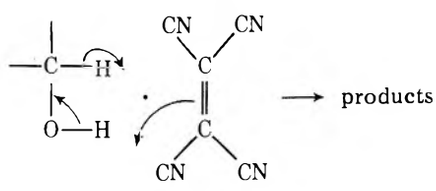
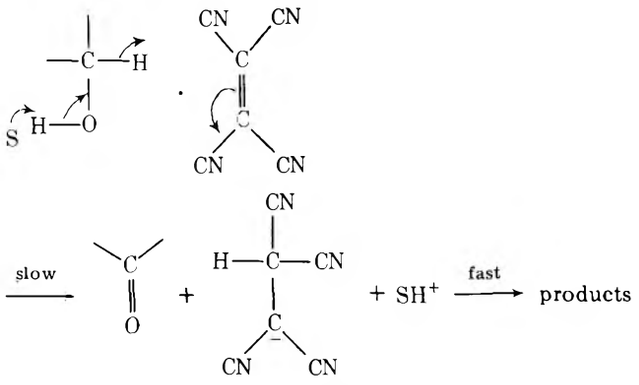


Table IV

Compd	Registry no.	τ 9.4 (CH_3)	τ 8.5 (CH_2)	τ 5.8 (CH)	τ 4.5 (OH)	τ 3.0 (Ph)
PhCH(OH)Et	93-54-91	3.2	2.0	1.1	0.9	5
PhCD(OH)Et	32047-42-0	3.0	2.2	0	1.0	5
PhCH(OD)Et	66303-46-6	3.0	1.9	1.2	0.1	5
PhCD(OD)Et	66303-45-5	3.3	2.0	0	0.3	5

Scheme VII



vincing because no primary kinetic isotope effect was observed in the transfer of the hydroxyl hydrogen of 1-phenylpropanol and the transition state is considered to be too strongly polarized for this cyclic concerted process. Scheme VII is a two-step mechanism, but the rate-limiting step is a concerted process involving a solvent as a proton acceptor. This scheme also is presumed not to be reasonable because the yield of the products of the dehydrogenation reaction was not correlated to the basicity of the reaction solvents and no primary isotope effect was observed on the transfer of the hydrogen atom of the hydroxyl group of the hydrogen donor. Furthermore, it is inferred that Scheme VII is less consistent with a highly charge-separated transition state than is Scheme V.

Experimental Section

Materials. 1,1,2,2-Tetracyanoethane,[5] 2-methyl-1-phenylpropanol,[23] 1,2-dihydro-1,1-dimethylnaphthalene,[24] and the *p*-methyl,[25] *p*-chloro-,[25] *m*-chloro,[25] *p*-bromo,[26] and *m*-bromo derivatives[27] of 1-phenylpropanol were prepared by the methods reported in the literature. All of the reagents purchased were purified by distillation or recrystallization.

Preparation of Deuterated 1-Phenylpropanols. To $LiAlD_4$ (0.4 g) in dry ether was added propiophenone dropwise with cooling by ice. The mixture was heated under reflux until the disappearance of the phenone was confirmed by GC analysis. After the addition of dilute sulfuric acid (10 mL) with cooling by ice, the organic layer was separated, washed with aqueous sodium carbonate solution and water, dried with sodium sulfate, and distilled. PhCD(OH)Et was obtained in a yield of 60%, and the boiling point at 15 mmHg was 109–112 °C.

By using deuterium oxide (10 mL) instead of dilute sulfuric acid, PhCD(OD)Et was obtained in 58% yield, and the boiling point at 15 mmHg was 93–96 °C.

To $LiAlD_4$ (1.2 g) in dry ether (40 mL) was added 1-phenylpropanol (4.0 g) dropwise with cooling by ice, and the mixture was heated under reflux for 1 h. It was cooled by ice, treated with deuterium oxide (10 mL), and heated for 1 h. Then the organic layer was separated, dried with sodium sulfate, and distilled. PhCH(OD)Et was obtained in 52% yield, and the boiling point at 18 mmHg was 109–112 °C: IR ν_{C-D} = 2100 cm^{-1} and ν_{O-D} = 2470 cm^{-1}.

Relative areas of the peaks of the 1-phenylpropanols in their ^1H NMR spectra, which were measured without solvent using Me_4Si as an internal standard, are given in Table IV.

An Example of Transfer Hydrogenation. 1-Phenylpropanol (13.8 μL, 0.1 mmol) was put into a Pyrex glass tube which had been sealed at one end. Dioxane was added, and the total volume of the solution was made to 0.5 mL. The tube was sealed under vacuum after a freeze–pump–thaw cycle at 10^{-3} Torr on a vacuum line in a liquid nitrogen bath. The sealed tube was heated in a polyethylene glycol bath kept at 100 ± 1 °C. To analyze the reaction mixture, GC was performed at 150 °C on a Hitachi 163 instrument equipped with a flame ionization detector using 10 μL of phenylcyclohexane as an internal standard. A 1 m × 6 mm stainless steel column packed with 12% diethylene glycol succinate on Diasolid L was used. The other transfer hydrogenations were carried out in a similar way.

An Example of Kinetic Measurements. Five sealed tubes that were prepared by the method described above were heated on a polyethylene glycol bath kept at 100 ± 1 °C for 30, 60, 90, 120, and 180 min, respectively. Each reaction mixture was submitted to GC analysis. The reaction rates were obtained by the gradiation of time against the yield of ketone plot.

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Preparation and Solvolysis of 2-Alkynyl-, 2-Cyclopropyl-, and 2-Arylallyl Alcohol Tosylates. 3.[1] Relationship Among Allyl and Cyclopropyl Cations

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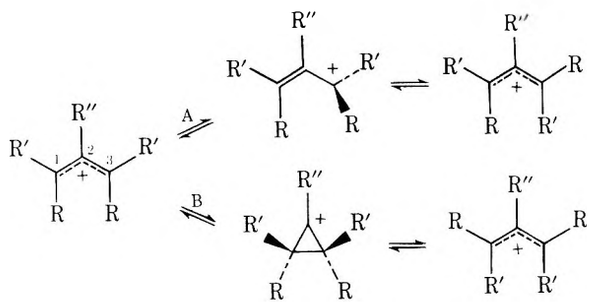
2-Phenylethynyl-, 2-cyclopropyl-, and 2-phenylallyl tosylates **3**, **4**, and **5** have been prepared. Their products of solvolysis in various solvents and their rates of ethanolysis were compared with those of 1-phenylethynyl-, 1-cyclopropyl-, and 1-phenylcyclopropyl tosylates **6**, **7**, and **8**, respectively. The theoretical expectations of the ring closure of 2-substituted allyl cations with efficient electron releasing groupings into stabilized cyclopropyl cations have not been proven experimentally by our results, but a limitation of the anchimeric assistance of the double bond in the solvolysis of allyl tosylates seems to result from the presence of such substituents. The solvolyses of 1-cyclopropyl- and 1-phenylcyclopropyl tosylates **7** and **8** have been reinvestigated.

The stereomutation of allyl cations can occur by two mechanisms involving either simple rotation about one of the C–C bonds (path A) or disrotatory closure to a cyclopropyl cation followed by disrotatory opening in the opposite sense (path B).[2]



Path A would be favored by carbocation stabilizing substitutents R, R′ at C_1 (or C_3), whereas path B would be favored by carbocation stabilizing substituents R″ at C_2.

Although all allyl cation stereomutations observed up to now have the substitution pattern required to proceed via path A and in fact have done so,[2-4] theoretical expectations however support path B.

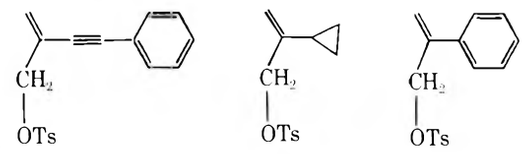
For example, calculations indicate that the 2-methylallyl cation (R = R′ = H; R″ = CH_3) should stereomutate through the 1-methylcyclopropyl cation since methyl substitution favors path B over path A by 18.5 kcal mol^{-1}.[4]

Thus, it can be expected that electron releasing substituents R″, which stabilize carbocations to a greater extent than methyl, might even render the 1-substituted cyclopropyl cations **1** more stable than their 2-substituted allyl counterparts **2**.[4]

1 **2**

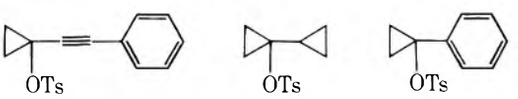
The reactions involving such stabilized cyclopropyl cations **1** (R″ = aryl,[5] cyclopropyl,[6,7] alkenyl,[8] alkynyl[1]) are known to proceed with only partial ring opening into allyl cations (**1** → **2**); however, no closure of 2-substituted allyl cations to 1-stabilized cyclopropyl cations has been reported yet (**2** → **1**).

We report here the solvolysis data of 2-substituted allyl tosylate derivatives **3** (R″ = –C≡CC_6H_5), **4** (R″ = cyclopropyl), and **5** (R″ = aryl) which have been investigated, in order to determine experimentally the effect of an efficient electron releasing substituent on the stabilization of the intermediate allyl cation **2**, and the eventual propensity of such 2-substituted allyl cations to undergo the ring closure into stabilized cyclopropyl cations **1**.



3 **4** **5**

The behavior of these 2-substituted allyl derivatives has been examined and compared to the behavior of their cyclopropyl counterparts **6**, **7**, and **8**, respectively.

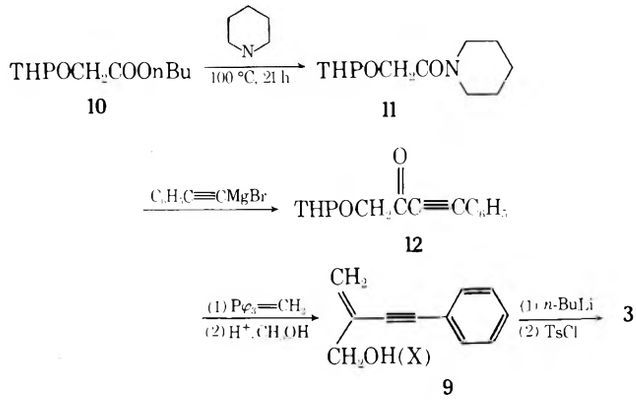


6 **7** **8**

Results and Discussion

Preparation of the 2-(Phenylethynyl)allyl Tosylate 3. Despite several attempts, we did not succeed in obtaining the allylic halogenation[9-11] or oxidation[9] of 2-methyl-4-phenyl-1-buten-3-yne (readily available from phenylacetylenemagnesium bromide and acetone). Then, the enynol **9** was synthetized from the tetrahydropyranyl ether of the *n*-butylglycolic acid ester **10**. Heating at 100 °C with piperidine **10** gave the amide **11**; the addition of phenylethynylmagnesium bromide provided the ketone **12** which underwent the Wittig reaction with methylenephosphorane to give, after treatment in acidic methanol, the expected enynol **9**. The normal pyridine procedure[12] did not lead to the tosylate derivative of enynol **9**; upon treatment at 0 °C with an equivalent of *n*-BuLi followed by the addition at −40 °C of tosyl chloride, the enynol **9** was finally converted into the expected tosylate **3**.

The syntheses of the 1-(phenylethynyl)-1-cyclopropanol



10 **11** **12** **9**

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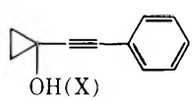
Table I. Solvolysis Products (%) of the Cyclopropyl Tosylates 6, 7, and 8 and Allyl Tosylates 3, 4, and 5, Comparatively[a]

	Registry no.		Temp, °C	Reaction time, h	 13. 22. 29	 9. 21. 30	Others[d]
6[b]	57951-60-7	Acetone–H_2O	70.0	48	73.5	26.5	
		(60:40)	70.0	120	69	25	6
		EtOH–H_2O	70.0	40	85[c]	15[c]	
		(50:50)					
		Trifluoroethanol	70.0	8	52	48	
			70.0	19	50	50	
3	66303-62-6	Acetone–H_2O	70.0	1.5		60	40
		(60:40)	70.0	60		57	43
		EtOH–H_2O	70.0	40		58[c]	42
		(50:50)					
		Trifluoroethanol	70.0	6		36	64
			70.0	19		37	63
7	32364-40-2	Acetone–H_2O, CO_3Ca	25.0	24	50	26	24
		(50:50)					
		Acetone–H_2O[h]	25.0	26	67		33[e]
		(50:50)					
		EtOH–H_2O, CO_3Ca	25.0	24	68.5[c]	31.5[c]	
		(50:50)					
		Trifluoroethanol	25.0	48	42.5[g]	19.5[g]	38
4	66303-63-7	Acetone–H_2O, CO_3Ca	25.0	60		90	10[f]
		(50:50)					
		Acetone–H_2O[h]	25.0	60			100
		(50:50)					
		EtOH–H_2O, CO_3Ca	50.0	10		100[c]	
		Trifluoroethanol	50.0	48		60[g]	40
		Hexafluoro-2-propanol	50.0	48		45	55
8	4382-80-3	Acetone–H_2O, CO_3Ca	50.0		23.5	76.5	
		(50:50)					
		Acetone–H_2O[h]			22	63	15
		(50:50)					
		EtOH–H_2O, CO_3Ca			32[c]	68[c]	
		Hexafluoroisopropyl alcohol				49	51
5	66303-64-8	Acetone–H_2O, CO_3Ca	50.0	15		89	11
		(50:50)					
		Acetone–H_2O[h]	50.0	15		91	9
		(50:50)					
		EtOH–H_2O, CO_3Ca	50.0	15		100[c]	
		(50:50)					
		Hexafluoro-2-propanol	50.0	24		43	57

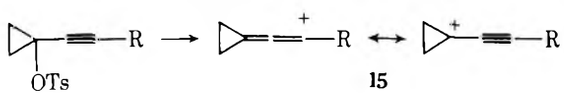
[a] If not specified, buffered with 1.1 equiv of triethylamine. [b] In part from ref 1. [c] As a mixture of the alcohol and its ethyl ether. [d] Mainly as nonidentified polymeric material. [e] With a trace (<5%) of cyclopropyl ethyl ketone. [f] Mainly as starting tosylate. [g] Low yield due to the formation of very volatile fluoro ethers. [h] Unbuffered.

(13) and 1-(phenylethynyl)-1-tosyloxycyclopropane (6) have been reported previously.[1]



13

Solvolysis of 2-(Phenylethynyl)allyl Tosylate 3 and of 1-(Phenylethynyl)-1-tosyloxycyclopropane (6), Comparatively. Our investigation of the chemistry of the cyclopropyl cation 1 began with the solvolysis of 1-alkynylcyclopropyl tosylates 14; the results were clearly consistent with a S_N1' ionization process involving anchimeric assistance of the triple bond and formation of the mesomeric cation 15,



14 15

highly stabilized by deloca ization of the positive charge over the three-carbon system.[1]

However, as evidenced by product distribution and kinetic data, the formation of 15 as an intermediate in the solvolysis of 14 appeared to be strongly dependent upon the nature of the substituent R and entailed an efficient electron-releasing substituent at the allenyl (or propargyl) end.

Thus for instance, the only products of aqueous ethanolysis of 14 (R = CH_3) were allylic derivatives from total cyclopropane ring opening; while only partial or no ring opening at all was observed from 14 (R = cyclopropyl) and 14 (R = *p*-anisyl), yielding 90 and 100% of unrearranged cyclopropanols (or derivatives), respectively.[1]

In order to compare the data, the tosylates 3 and 6 were solvolyzed in solvents of different ionizing power and nucleophilicity, buffered with 1.1 equiv of triethylamine to avoid any acid-catalyzed rearrangement of the products[6] and at a temperature low enough (i.e., 70 °C) to avoid the subsequent homoketonization of the cyclopropanols.[1,13]

As shown by the product distribution listed in Table I, the allylic tosylate 3 did not undergo the expected ring closure into the cyclopropanol (or derivatives) 13 (R = $-C{\equiv}CC_6H_5$) but merely yielded, upon solvolysis, the unrearranged allylic alcohol 9 and undefined polymeric compounds. The lack of 13 (or of its derivatives) in the crude product of the solvolysis of 3 was carefully checked by GLC, TLC, and spectroscopic

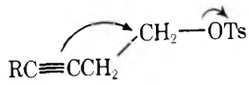
Table II. Solvolysis Rates of the Cyclopropyl Tosylates and Allyl Tosylates, Comparatively

	Solvent[a]	Temp, °C	$k^b \times 10^4$ s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	m
6[c]	50E	70.0	0.83 ± 0.02	19.67	−20.10	0.58
3	50E	70.0	9.91 ± 0.02	25.81	2.65	0.67
	50E	60.0	3.08 ± 0.05			
	60E	70.0	4.82 ± 0.02			
7[d]	50E	70.0	2915			
	80E	35.0	4.23 ± 0.01	21.08	−5.60	0.77
4	50E	70.0[f]	173.99			
	50E	60.0	56.02 ± 0.04	25.10	6.29	0.49
	50E	50.0	18.17 ± 0.02			
	60E	60.0	33.32 ± 0.03			
8	50E	70.0	86.55 ± 0.07	23.23	−0.53	0.37[g]
	50E	60.0	30.19 ± 0.05			
	60E	70.0	58.11 ± 0.08			
5	50E	70.0	37.84 ± 0.04	20.23	−10.93	0.30[g]
	50E	60.0	15.07 ± 0.04			
	60E	70.0	27.38 ± 0.03			
37[e]	100A[e]	100.1	0.13 ± 0.02	28.7	−4.6	
38[f]	70D[f]	50.0	1.06	19.3	−13.82	

[a] 50E refers to 50% aqueous ethanol v/v before mixing. [b] The errors reported were determined by means of a least-squares computer program. [c] From ref 1. [d] From ref 7. [e] From ref 26; 100A refers to 100% anhydrous acetic acid. [f] From ref 33; 70D refers to 70% aqueous dioxane. [g] The m values for allyl chloride and benzylic tosylate solvolysis are 0.40 and 0.39, respectively, in aqueous ethanol.[31]

analysis. Under the same conditions, however, the tosyloxycyclopropane **6** was reported to solvolyze with the formation of a mixture of the unrearranged cyclopropanol **13** and of the open ring allylic derivative **9**.[1] This result shows clearly that whatever the ionizing power and the nucleophilicity of the solvent the mesomeric carbocation **15** is not involved in the solvolysis of the allylic tosylate **3**.

On the other hand, these results can appear consistent with a triple bond participation. Indeed, such an anchimeric assistance has been previously reported for homopropargylic tosylates; thus, the cyclopropylidenemethylcation **17** was

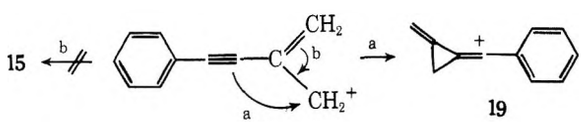


16

17

proposed as an intermediate in the homopropargylic rearrangement of the tosylate **16**.[14]

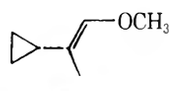
In this way, the triple bond participation in the solvolysis of the tosylate **3** would involve the intermediate vinyl cation **19**. As the parent 1,2-dimethylenecyclopropane itself was reported to be a very labile small ring compound which undergoes polymerization readily at −10 °C,[15] it does not appear unlikely that the homopropargyl rearrangement of **3** led, via cation **19**, to undefined polymeric compounds.



18

As shown in Table II the solvolysis rates of the tosylates **3** and **6** in aqueous ethanol were measured by automatic continuous titration at pH 7.0. It seems likely that the homopropargylic assistance of the triple bond (path a) reduces, in stabilizing by charge delocalization the intermediate carbocation **18**, the anchimeric assistance of the allylic double bond (path b) and thereby prevents the expected cyclization of ion **18** into the mesomeric carbocation **15**.

Preparation of the 2-Cyclopropylallyl Tosylate 4 and of the 1-Cyclopropylcyclopropyl Tosylate 7. The addition of the methoxymethylenetriphenylphosphorane on the cyclopropyl methyl ketone provided the enol ether **20**, which on addition of singlet oxygen[16] and hydride reduction led to the 2-cyclopropylallyl alcohol **21**. Inert to the normal pyridine procedure,[12] the allylic alcohol **21** was converted into the tosylate **4** upon treatment with n-BuLi and tosyl chloride at −40 °C.



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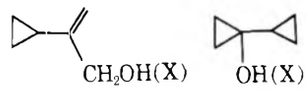
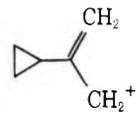


21 **22** **23**

The reaction of the hemiketal of cyclopropanone,[17] now readily available,[1] with 2 equiv of cyclopropylmagnesium bromide provided the 1-cyclopropylcyclopropanol (**22**) in high yield, which was converted into the tosylate **7** by the normal pyridine procedure.[12]

Solvolysis of 2-Cyclopropylallyl Tosylate 4 and of 1-Cyclopropyl-1-tosyloxycyclopropane (7), Comparatively. Taking into account the high effectiveness of the cyclopropane ring for stabilizing an adjacent carbocation,[18] the allyl tosylate **4** was solvolyzed in order to determine the propensity of the allyl cation **24** to undergo the ring closure (**24** → **25**).



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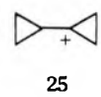


25

Furthermore, an apparently facile acid-catalyzed rearrangement of the 2-cyclopropylallyl alcohol **21** into the cyclopropyl ethyl ketone **23** had been recently claimed by Howell and Jewett.[7] So, they have reported that the buffered ($CaCO_3$) solvolysis of **7** afforded a mixture of allylic and cyclopropyl alcohols **21** and **22**, while unbuffered (TsOH) solvolysis yielded a mixture of alcohol **22** and ketone **23**. But, when subjected to the conditions of the unbuffered solvolysis, by addition of TsOH, the mixture of alcohols **21** and **22** was converted to the same mixture of products (**22** + **23**), obtained directly from the unbuffered solvolysis.

To explain the acid rearrangement of the allylic alcohol **21** into the ketone **23**, the ring closure of carbocation **24** → **25** could then be envisaged.

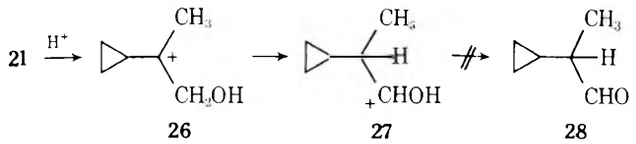
In view of this experimental fact and of the theoretical expectations[2-4] it appeared to us of interest to undertake this investigation. Thus, in order to compare the data, the tosylates **4** and **7** were solvolyzed in solvents of different ionizing power and nucleophilicity. As shown by the product distribution, listed in Table I, the allyl tosylate **4** solvolysis offered no detectable (GLC, NMR) amount of the product expected from the ring closure, i.e., 1-cyclopropylcyclopropanol (**22**) but only 2-cyclopropylallyl alcohol **21** (or its derivatives) even with a solvent of high ionizing power and low nucleophilicity such as 1,1,1,3,3,3-hexafluoroisopropyl alcohol.[19] Under the same conditions however, the cyclopropyl tosylate **7** solvolysis yielded a mixture of the unrearranged 1-cyclopropylcyclopropanol (**22**) and of the allylic alcohol **21** from ring opening.

The lack of cyclopropanol **22** in the solvolysis products of the allylic tosylate **4** shows clearly that, in spite of its very effective carbocation stabilizing power,[18] the cyclopropane ring, as substituent at C_2 of the allyl cation **2**, is not able to induce the expected ring closure **24** → **25**.

Moreover, we found the unbuffered solvolysis of the cyclopropyl tosylate **7** offers only a trace of ketone **23** (from IR and NMR spectroscopy of the crude solvolytic product). Furthermore, when subjected to the conditions of the unbuffered solvolysis, i.e., mixed with aqueous acetone containing either 0.1 or 1 equiv of *p*-toluenesulfonic acid, a pure sample of the 2-cyclopropylallylic alcohol **21** does not undergo the rearrangement into cyclopropyl ethyl ketone (**23**), as claimed by Howell and Jewett,[7] but yielded only undefined heavy alcoholic compounds, where cyclopropane rings are still present.

The reaction was easily followed by NMR, using a mixture of D_2O–deuterioacetone as solvent, containing 1 equiv of TsOH; after 45 min at 25 °C the signals of the olefinic protons of **21** around δ 4.60–4.82 ppm nearly vanished while the expected characteristic signals of the protons of the ketone **23** (i.e., a quartet around δ 2.30–2.67 ppm and a triplet around δ 0.87–1.15 ppm) were not detected. It must be emphasized that the cyclopropyl ethyl ketone (**23**) is really stable in acidic medium;[6] so, treated under the same conditions, a sample of ketone **23** was recovered unaltered and no measurable H–D exchange was detected.

Thus, contrary to the claim of Howell and Jewett[7] a revision of the generally accepted mechanism for the homoketonization of cyclopropanols[13] does not seem to be required. On the other hand, Mc Kinney and So have reported that the protonation, in acid solution, of the double bond of the 2-phenylallyl alcohol led to 2-phenylpropionaldehyde;[20] in the same way, the protonation of the double bond of **21** would lead, via carbocations **26** and **27**, to 2-cyclopropylpropionaldehyde (**28**).

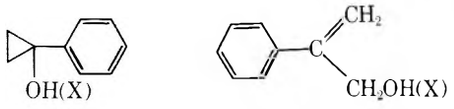


26 27 28

The lack of aldehyde **28** was readily checked (NMR, IR) either in the acid solution of allylic alcohol **21** or in the unbuffered solvolysis products of the tosylates **4** and **7**.

The solvolysis rates of the tosylates **4** and **7** in aqueous ethanol were measured by automatic continuous titration at pH 7.0, and the activation parameters were calculated as shown in Table II. These results confirm that the 1-cyclopropylcyclopropyl cation **25** is not involved in the solvolysis of the allyl tosylate **4**, i.e., the expected ring closure **24** → **25** did not occur, and provide a straightforward demonstration of the higher efficiency of the cyclopropane ring over the double bond to stabilize an adjacent electron deficiency.

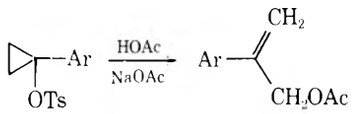
Preparations of the 1-Phenylcyclopropyl Tosylate 8 and of the 2-Phenylallyl Tosylate 5. The reaction of the hemiketal of cyclopropanone[1,17] with 2 equiv of phenylmagnesium bromide provided the 1-phenylcyclopropanol **29** in high yield. The oxidation of α-methylstyrene with selenium dioxide in acetic acid–acetic anhydride and reduction of the acetate ester with lithium aluminum hydride led to the 2-phenylallyl alcohol **30**.[20,21]



29 30

The cyclopropanol **29** was converted into the tosylate **8** by the normal pyridine procedure;[12] while the allylic alcohol **30** was converted into the tosylate **5** upon treatment with *n*-BuLi and tosyl chloride at −40 °C.

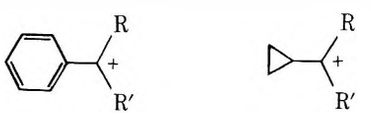
Solvolysis of 2-Phenylallyl Tosylate 5 and of 1-Phenyl-1-tosyloxycyclopropane (8), Comparatively. It has been reported by Depuy et al. that 1-arylcyclopropyl *p*-toluenesulfonates **31** readily undergo solvolysis in dry acetic acid–sodium acetate solution.[22]



31 32

The products of the solvolysis were allyl acetates **32** and no 1-arylcyclopropyl acetates were detected, although stable to the reaction conditions. A concerted process, with disrotatory ring opening occurring in the transition state of the reaction, was put forward to take into account these solvolysis data.[13,22] Steric or direct conjugative interactions were invoked to explain the few examples of limited ring opening reported in the solvolysis of 1-arylcyclopropyl tosylates.[5]

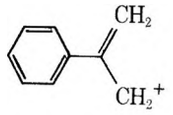
Disparity in the relative abilities of phenyl and cyclopropyl groups to stabilize an empty p orbital on an adjacent carbocation center were reported in the literature. Thus, for example, from ^{13}C shielding measurements Olah has concluded that the aromatic grouping is far superior to the cyclopropane ring in stabilizing a carbocation.[23] This stipulation is however at odds with the formation rates of the tertiary carbocations **33** and **34** determined by Brown from solvolysis data.[24]



33 34

In fact, recent combined experimental and theoretical investigatons have clearly depicted, in the lack of steric inhibition of conjugation, the phenyl group as the more effective stabilizing substituent by 20 kcal/mol for a primary carbocation (R = R′ = H) and roughly by 10 kcal/mol for a secondary cation (R = H; R′ = CH_3), while in reverse the Walsh orbitals of cyclopropane are slightly superior (0.8 kcal) to the phenyl π system in stabilizing a tertiary carbocation center (R = R′ = CH_3).[25]

In view of these results and within the framework of our investigation it appears to us of interest to reexamine the solvolytic behavior of 1-phenylcyclopropyl tosylate (**8**) in other solvents than acetic acid, in order to compare the stabilizing effect of the phenyl and cyclopropane rings to the cyclopropyl carbocations **36** and **25**, respectively. On the other hand, the solvolytic behavior of 2-phenylallyl tosylate **5** was investigated in order to determine the propensity of the carbocation ring closure (**35** → **36**).



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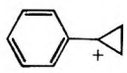

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As shown by the product distribution, listed in Table I, the 1-phenylcyclopropyl tosylate (8) solvolyzes with the formation of a mixture of the unrearranged cyclopropanol (or ether derivatives) **29** (R = C_6H_5) and of the open ring allylic derivatives **30.** As expected, the electron donating effect of the phenyl ring is effective in stabilizing the electron deficiency of the cyclopropyl carbocation **36** and, as a matter of fact, in limiting the opening of the cyclopropane ring.

On the other hand, the lack of cyclopropanol **29** in the solvolysis products of the 2-phenylallyl tosylate **5** confirms our previous findings that neither the σ bonds of the cyclopropane ring itself (vide supra) nor the electron-donating power of the π phenyl system are efficient enough to favor the expected ring closure: allyl cation **35** → cyclopropyl cation **36.**

The comparison of the solvolysis product ratios of unrearranged cyclopropanols/open ring allyl derivatives (e.g., 68.5/31.5 and 32/68 in aqueous ethanol, respectively) listed in Table I shows clearly that the cyclopropane ring is more effective than the phenyl group in stabilizing the cyclopropyl cation. These results are confirmed by the kinetic data listed in Table II. Thus, the 1-phenylcyclopropyl tosylate reacted 3×10^{-2} times slower than the 1-cyclopropylcyclopropyl tosylate **(7).**

Conclusion. The m values listed in Table II, which are a measure of the sensitivity of the substrates to changes in solvent ionizing power Y,[27] fall in the range normally found for k_s and k_Δ processes.[28] From the low propensity of the parent cyclopropyl tosylate itself to changes in solvent nucleophilicity, it has been reported that the solvolyses of cyclopropyl derivatives are mainly k_Δ processes (m = 0.508) where the electrons from the breaking cyclopropane bond take the place of the attacking nucleophile.[26] Such an anchimeric assistance can be provided, however, by an efficient electron releasing substituent and thereby the ring opening of the cyclopropyl moiety is reduced, or even suppressed totally.[1,6,7]

The anchimeric assistance of the substituent seems to be effective too in the solvolysis of the allyl tosylates **3, 4,** and **5** but, unfortunately, this k_Δ process has the effect of limiting by further charge delocalization the assistance of the allylic double bond and thereby the expected ring closure in stabilizing the intermediate carbocations **18** by homopropargylic type assistance,[14] **24** by homocyclopropylcarbinyl type assistance,[29] and **35** by phenonium type assistance.[30]

Although the formation of stabilized cyclopropyl cations has been proved to occur in the solvolysis of suitably substituted cyclopropyl derivatives and the ^{13}C shielding measurements of a cyclopropyl cation have even been reported recently by Olah et al.,[32] the theoretical expectations of the 2-substituted allyl cation ring closure **2** → **1** have not been proven experimentally.

Experimental Section

2-Tetrahydropyranyl Ether Glycolamide (11). A solution of 10.8 g (0.05 mol) of n-butyltetrahydropyranyl glycolate and 16 mL of piperidine was heated at 100 °C. The reaction was followed by IR; after 21 h at 100 °C the ester carbonyl stretching at 1760 cm^{-1} completely disappeared and the amide band appeared at 1655 cm^{-1}. The piperidine excess was removed under vacuum; distillation at reduced pressure of the crude product gave 7.5 g (70%) of **11:** bp 110 °C (0.035 mm); IR (neat) $\nu_{C=O}$ 1655 cm^{-1}; NMR (CCl_4) δ 1.65 (m, 12 H), 3.45 (m, 6 H), 4.10 (d, 2 H), and 4.62 (m, 1 H).

4-Phenyl 1-Tetrahydropyranyl Ether 3-Butyn-2-one (12). To 12.31 g (0.06 mol) of phenylacetylenemagnesium bromide[34] in 50 mL of tetrahydrofuran was added with stirring at room temperature a solution of 7.5 g (0.033 mol) of glycolamide 11 in 20 mL of tetrahydrofuran. The mixture was stirred for 1 h at room temperature and heated under reflux for 2 h. The cold mixture was poured on a mixture of 60 mL of sulfuric acid (1 N) and 100 g of crushed ice and extracted with ether. The organic layer was washed with water, dried over magnesium sulfate, and concentrated to yield a light yellow oil. Distillation at reduced pressure gave a mixture of piperidine and phenylacetylene [bp 30–40 °C (10 mm)] and 2.9 g of glycolamide **11** [bp 110 °C (0.035 mm)]. The residue (8 g) was dissolved in a minimum amount of diethyl ether and placed on a silica gel column (200 g of silica gel 70–230 mesh) and eluted with 25 vol % diethyl ether in pentane, giving 1 g of unidentified product, 0.6 g of glycolamide 11, 1.1 g of 4-phenyl-2-oxo-3-propynol, 0.6 g of N-(2-hydroxyacetyl)-piperidine, and 3.7 g (46%) of 4-phenyl 1-tetrahydropyranyl ether 3-butyn-2-one (**12**): IR (neat) 2210 ($\nu_{C\equiv C}$) and 1690 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4) δ 1.15 (m, 6 H), 3.55 (m, 2 H), 4.30 (s, 2 H), 4.80 (m, 1 H), and 7.50 (m, 5 H).

2-(Phenylethynyl)allyl Alcohol 9. To 2.93 g (8.2 mmol) of methyltriphenylphosphonium bromide suspended in 60 mL of dry benzene was added with stirring 0.92 g (8.2 mmol) of potassium *tert*-butylate, at room temperature, under dry N_2. The mixture was refluxed for 1 h. The yellow solution was then cooled to 0 °C and a solution of 1 g (4.1 mmol) of butynone **12** in 10 mL of benzene was added. The yellow color was discharged and the solution was allowed to warm to room temperature and stirred for a further 2 h and then refluxed for 30 mn. The resulting deep-red mixture was washed with water, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel eluting with ether–light petroleum (20:80) to give an enyne (850 mg, 86%): IR (neat) 2220 ($\nu_{C\equiv C}$) and 1673 cm^{-1} ($\nu_{C=C}$); NMR (CCl_4) δ 1.60 (m, 6 H), 3.60 (m, 2 H), 4.15 (m, 1 H), 4.80 (m, 1 H), 5.60 (m, 1 H), and 7.30 (m, 5 H).

A solution of 800 mg of the enyne in 5 mL of methanol containing 2 drops of 1 N sulfuric acid was stirred at room temperature for 15 min. The solution is then washed with sodium bicarbonate and water and dried over magnesium sulfate, and the methanol was removed under vacuum. Fractional distillation of the crude material yielded 0.5 g (97%) of the 2-(phenylethynyl)allyl alcohol **9:** bp 96–98 °C (0.008 mm); IR (CCl_4) 3630 and 3350 (ν_{OH}), 2210 ($\nu_{C\equiv C}$), and 1620 cm^{-1} ($\nu_{C=C}$); NMR (CCl_4) δ 2.80 (m, 1 H), 4.15 (m, 2 H), 5.60 (m, 2 H), and 7.33 (m, 5 H); MS M^+ m/e (rel intensity) 158 (8.5), 153 (10), 152 (12.5), 141 (8), 127 (12.5), 119 (99), 117 (100), 105 (10), 94 (14), 84 (10), 82 (14), 47 (15).

2-(Phenylethynyl)allyl Tosylate 3. A solution of 0.316 g (2 mmol) of the enynol **9** in 5 mL of tetrahydrofuran was placed in a 50-mL reaction flask, flushed with argon, and fitted with a side arm with a rubber serum cap. At 0 °C was added dropwise 2 mmol (1.27 mL of a 1.575 N solution in hexane) of n-butyllithium. The reaction mixture was stirred for 2 h and then cooled to −40 °C (dry ice + acetonitrile bath). Next, a solution of 0.382 g (2 mmol) of p-toluenesulfonyl chloride in 2 mL of tetrahydrofuran was added and stirred for 15 min at −40 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction mixture was cooled to 0 °C and then placed in a separatory funnel and washed rapidly with cold 5% sodium bicarbonate solution. The organic layer was decanted and dried over anhydrous magnesium sulfate and the solvent was removed. The residue was chromatographed on silica gel eluting with ether–light petroleum (5:95) to give 0.540 g (87%) of the pure 2-(phenylethynyl)allyl tosylate **3** as a pale yellow oil: NMR (CCl_4) δ 2.35 (s, 3 H), 4.55 (s, 2 H), 5.55 (s, 2 H), 7.30 (s, 5 H), and 7.20–7.87 (q, 4 H). Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16; S, 10.26. Found: C, 68.94; H, 5.25; S, 9.97.

1-Cyclopropylcyclopropanol (22). The preparation and description of **22** have been previously reported.[7,35,36] More conveniently, **22** has been obtained by the addition at room temperature of 16.83 g (0.16 mol) of cyclopropanone hemiketal[1] to 48.52 g (0.33 mol) of cyclopropylmagnesium bromide in 150 mL of tetrahydrofuran. The reaction mixture was stirred for 2 h at room temperature and heated under reflux for 4 h. After the usual workup the cyclopropanol **22** was obtained in 88% yield.

1-Cyclopropyl-1-tosyloxycyclopropane (7). The tosylate **7** was obtained in 74% yield by conventional means through the reaction of the alcohol **22** with tosylchloride in pyridine at 0 °C.[12] Two recrystallizations from pentane gave the pure 1-cyclopropyl-1-tosyloxycyclopropane (**7**): mp 39 °C; NMR (CCl_4) δ 0.15–1.40 (m, 8 H), 1.70 (m, 1 H), 2.53 (s, 3 H), and 7.30–7.90 (q, 4 H). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.89; H, 6.39; S, 12.43. Found: C, 62.04; H, 6.56; S, 12.42.

2-Cyclopropylallyl Alcohol 21. Method A.[7] A solution of 9 g (35.7 mmol) of the tosylate **7** in 60 mL of acetic acid buffered with 3.22 g (39.3 mmol) of sodium acetate was stirred at room temperature for 60 h. The mixture was concentrated by removing acetic acid under

vacuum and extracting with ether. The extract was washed with two 75-mL solutions of 1 N sodium hydroxyde and twice with water and then dried over magnesium sulfate. The solvent was evaporated and the NMR spectrum of the crude product (3.6 g, 72%) showed the formation of two products: 1-cyclopropyl-1-acetoxycyclopropane (28%) and 2-cyclopropylallyl acetate (72%). The acetates were converted to the alcohols with lithium aluminum hydride, and the alcohols separated by preparative liquid chromatography to yield cyclopropanol **22** and 2-cyclopropylallyl alcohol **21**: IR (CCl_4) 3620 and 3450 (ν_{OH}), 3090 (ν_{CH}), and 1645 cm^{-1} ($\nu_{C=C}$); NMR (CCl_4) δ 0.5 (m, 4 H), 1.20 (m, 1 H), 2.10 (s, 1 H), 4.00 (s, 2 H), 4.65 (m, 1 H), and 4.85 (m 1 H); MS M^+ *m/e* (rel intensity) 98.2 (26.8), 83.2 (20.6), 79.1 (91.7), 69.1 (34.5), 57.1 (39.5), 39.2 (100).

Method B.[16] The enol ether **20** has been prepared in 90% yield from cyclopropyl methyl ketone and methoxymethylenetriphenylphosphorane by the procedure of Corey.[37] A solution of 0.08 mol of enol ether **20** in 60 mL of benzene containing 15 mg of *meso*-tetraphenylporphine was irradiated in a current of oxygen for 15 min, following a recently reported procedure.[38] The benzene was removed on a rotary evaporator and the residue was dissolved in 20 mL of ether. To the etheral solution were added at −5 °C 2 equiv of lithium aluminum hydride with stirring. After the usual workup 2-cyclopropylallyl alcohol **21** was isolated by preparative GLC in 60% yield.

2-Cyclopropylallyl tosylate 4 was prepared analogously to the tosylate **3** by the reaction of 262 mg (2.7 mmol) of the allyl alcohol **21** with 1 equiv of *n*-BuLi at 0 °C followed by the addition of 500 mg (2.68 mmol) of tosyl chloride at −40 °C. After workup (excess of alcohol **21** can be removed under vacuum, 0.05 mm), 500 mg (72%) of practically pure tosylate **4** was yielded as a pale yellow oil: NMR (CCl_4) δ 0.55 (m, 4 H), 1.20 (m, 1 H), 2.48 (s, 3 H), 4.55 (s, 2 H), 4.90 (s, 1 H), 5.05 (m, 1 H), 7.45–8.05 (q 4 H). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.89; H, 6.39; S, 12.43. Found: C, 62.17; H, 6.54; S, 12.31.

1-Phenylcyclopropanol 29. To phenylmagnesium bromide prepared from 31.4 g (0.2 mol) of bromobenzene and 4.86 g (0.2 mol) of magnesium metal in 150 mL of anhydrous tetrahydrofuran was added dropwise a solution of 10.2 g (0.1 mol) of cyclopropanone hemiketal.[1] The reacting mixture was stirred at room temperature overnight. After the usual workup, 13.4 g (100%) of pratically pure 1-phenylcyclopropanol was obtained: NMR δ 0.85 (m, 2 H), 1.05 (m, 2 H), 4.10 (m, 1 H), and 7.15 (m, 5 H).

1-Phenyl-1-tosyloxycyclopropane (**8**) was prepared by the normal pyridine procedure.[12] Two recrystallizations from pentane at −60 °C gave the pure 1-phenyl-1-tosyloxycyclopropane (**8**): mp 73.1 °C; NMR (CCL_4) δ 1.10 (m, 2 H), 1.60 (m, 2 H), 2.32 (s, 3 H), 7.18 (m, 5 H), and 6.98–7.50 (q, 4 H). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.82; H, 5.72; S, 10.83.

2-Phenylallyl Alcohol 30. The oxidation of α-methylstyrene with selenium dioxide in acetic acid–acetic anhydride yielded 36% of 3-acetoxy-2-phenyl-1-propane: bp 60–61 °C (0.085 mm) [lit.[21] bp 112–113 °C (5 mm)]; NMR (CCl_4) δ 1.95 (s, 3 H), 4.90 (s, 2 H), 5.30 (m, 1 H), 5.47 (m, 1 H), and 7.30 ppm (m, 5 H). The acetate was reduced with lithium aluminum hydride as usual and the crude product was distilled: bp 73 °C (0.25 mm); IR (neat) 3350 (ν_{OH}) and 1632 cm^{-1} ($\nu_{C=C}$); NMR (CCl_4) δ 3.20 (m, 1 H), 4.32 (s, 2 H), 5.25 (m, 1 H), 5.35 (m, 1 H), and 7.25 (m, 5 H); MS M^+ *m/e* (rel intensity) 134.2 (73.2), 115.1 (26.5), 104.1 (13.8), 103.1 (97.9), 102.2 (20.4), 92.1 (81.8), 91.1 (60.8), 77.1 (100.0).

2-Phenylallyl tosylate 5 was prepared analogously to the tosylate **3** by the reaction of 1.5 (11.25 mmol) of the alcohol **30** with 1 equiv of *n*-BuLi at 0 °C, followed by the addition of 2.15 g (11.30 mmol) of tosyl chloride at −40 °C in tetrahydrofuran. After workup was obtained 2 g of a mixture containing only 30% of tosylate **5**. The mixture was chromatographed on silica gel eluting with ether–light petroleum (5:95) to give 500 mg (16%) of the pure 2-phenylallyl tosylate **5**: NMR (CCl_4) δ 2.40 (s, 3 H), 4.82 (s, 2 H), 5.32 (s, 1 H), 5.48 (s, 1 H), 7.22 (s, 5 H), and 7.20–7.78 (q, 4 H). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64: H, 5.59; S, 11.12. Found: C, 65.89; H, 5.69; S, 11.21.

Description of a Typical Comparative Product Analysis. The tosylates **4** and **7** (125 mg, ~0.5 mmol) were dissolved in 2.5 mL of acetone–H_2O (50:50) containing 1.1 equiv of calcium carbonate as buffer, respectively. The solvolysis mixtures were heated in sealed tubes at 25 °C for 40 h. After cooling the tubes were opened and the mixture was poured into 100 mL of ether. The etheral extract was washed with 5 mL of aqueous NaCl solution and with water and then dried with water and then dried over anhydrous magnesium sulfate. The solvent was removed by a short-path distillation. The crude solvolysis mixtures were worked up by preparative gas chromatography or thin layer chromatography, and the products of each solvolysis were identified comparatively by combined GC and MS analysis and from their IR and NMR spectra.

The other solvolysis reactions were run in the same way, under the conditions reported in Table I.

1-(Phenylethynyl)cyclopropanol 13 (R = $-C{\equiv}CC_6H_5$) has been described.[1]

1-Ethoxy-1-(phenylethynyl)cyclopropane 13 (R = $-C{\equiv}CC_6H_5$; X = $-CH_2CH_3$) has been described.[1]

1-(2′,2′,2′-Trifluoroethoxy)-1-(phenylethynyl)cyclopropane 13 (R = $-C{\equiv}CC_6H_5$, X = $-CH_2CF_3$) has been described.[1]

1-Ethoxy-3-methylene-4-phenyl-3-butyne 9 (R = $-C{\equiv}CC_6H_5$; X = $-CH_2CH_3$) has been described.[1]

1-(2′,2′,2′-Trifluoroethoxy)-2-methylene-4-phenyl-3-butyne 9 (R = $-C{\equiv}CC_6H_5$; X = $-CH_2CF_3$) has been described.[1]

2-Cyclopropyl-3-ethoxy-1-propene 21 (X = CH_2CH_3): NMR (CCl_4) δ 0.35–0.75 (m, 4 H), 1.10 (m, 1 H), 1.20 (t, 3 H, J = 7.10 Hz), 3.60 (q, 2 H, J = 7.10 Hz), 3.85 (m, 2 H), 4.68 (m, 1 H), and 4.82 (m, 1 H); MS M^+ *m/e* (rel intensity) 126.1 (0.3), 111.3 (0.8), 98.3 (14.1), 67.2 (32.3), 39.2 (100.0).

2-Cyclopropyl-3-(2′,2′,2′-trifluoroethoxy)-1-propene 21 (X = CH_2CF_3): NMR (CCl_4) δ 0.40–0.90 (m, 4 H), 1.30 (m, 1 H), 3.80 (q, 2 H, J = 8.65 Hz), 4.05 (m, 2 H), 4.82 (m, 1 H), and 4.90 (m, 1 H); MS M^+ *m/e* (rel intensity) 180.1 (26.5), 165.0 (37.0), 139.1 (45.9), 80.1 (46.1), 79.0 (100.0), 67.1 (36.3), 41.1 (53.8).

2-Cyclopropyl-3-(1′,1′,1′,3′,3′,3′-hexafluoroisopropoxy)-1-propene 21 (X = $CH(CF_3)_2$): NMR (CCl_4) δ 0.40–0.90 (m, 4 H), 1.40 (m, 1 H), 4.25 (h, 1 H, J = 6 Hz), 4.35 (s, 2 H), 4.98 (m, 1 H), and 5.05 (m, 1 H); MS M^+ *m/e* (rel intensity) 248.1 (21.6), 233.2 (29.6), 207.0 (23.6), 82.1 (15.8), 81.1 (34.0), 80.1 (36.5), 79.1 (100.0), 69.0 (53.2), 67.1 (30.1).

1-Cyclopropyl-1-(2′,2′,2′-trifluoroethyl)cyclopropane 22 (X = CH_2CF_3): NMR (CCl_4) δ 0.25–1.50 (m, 9 H) and 3.80 (q, 2 H, J = 8.65 Hz); MS M^+ *m/e* (rel intensity) 180.1 (25.1), 165.0 (30.6), 139.0 (42.2), 80.1 (44.9), 79.0 (100.0), 41.1 (49.4).

Addition of *p*-Toluenesulfonic acid to 2-Cyclopropylallyl Alcohol 21. (a) One equivalent of TsOH. To a solution of 98 mg (1 mmol) of alcohol **21** in 2 mL of aqueous acetone (50:50) was added 190.2 mg (1 mmol) of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at 25 °C for 24 h and then poured into 100 mL of ether. The extract was washed with water and dried over magnesium sulfate and the ether was removed by a short-path distillation to yield 98 mg (100%) of residue.

The ^1H NMR spectrum of the crude product was quite complex and showed three multiplets at 0.40, 1.0, and 3.60 ppm and two singlets at 1.15 and 3.48 ppm; the IR (CCl_4) showed a very strong ν_{OH} at 3400 and a very sharp ν_{CH} (cyclopropane) at 3092 cm^{-1}. The lack of cyclopropyl ethyl ketone[35] [IR (neat) 1696 cm^{-1} $\nu_{C=O}$; NMR (CCl_4) δ 0.90 (m, 4 H), 1.10 (t, 3 H, J = 8.25 Hz), 1,80 (m, 1 H), and 2.55 (q, 2 H, J = 8.25 Hz); MS M^+ *m/e* (rel intensity) 98 (16.5), 69 (100), 57 (7.8), 41 (54), 39 (31.4)] was clearly established and confirmed by TLC and GC analysis.

(b) One-Tenth Equivalent of TsOH. In the same manner, to a solution of 98 mg (1 mmol) of **21** in 2 mL of H_2O–acetone (50:50) was added 19 mg (0.1 equiv) of TsOH, H_2O. The mixture was stirred for 24 h at 25 °C and yielded, after workup, the same polymeric mixture containing ~15% of allylic alcohol **21**.

(c) Into D_2O–CD_3COCD_3. A solution of 49 mg (0.5 mmol) of **21** in 0.4 mL of D_2O–hexadeuterio acetone (50:50) was placed in a NMR tube and the ^1H NMR spectrum was recorded: δ 0.4 (m, 4 H), 1.15 (m, 1 H), 3.90 (s, 2 H), 4.55 (s, 1 H), and 4.75 (m, 1 H). Then, 95 mg (0.5 mmol) of *p*-toluenesulfonic acid monohydrate was added to the NMR tube and the spectra were recorded, showing for the allylic + methylenic protons of **21** vs. the aromatic protons of TsOH a ratio equal to 61.5% after 3 min and roughly to 10% after 45 min, at 36 °C. But the characteristic signals of the cyclopropyl ethyl ketone (**23**) were not recognized in the spectra.

Addition of *p*-Toluenesulfonic Acid to Cyclopropyl Ethyl Ketone (23). A solution of 49 mg (0.5 mmol) of ketone **23** in 0.4 mL of D_2O–hexadeuterio acetone (50:50) was placed in a NMR tube and the ^1H NMR spectrum was recorded: δ 0.90–1.0 (m 4 H), 1.05 (t, 3 H, J = 7.35 Hz), 2.10 (m, 1 H), and 2.65 (q, 2 H, j = 7.35 Hz). Then 95 mg (0.5 mmol) of *p*-toluenesulfonic acid monohydrate was added to the NMR tube and the spectra were recorded every 15 min at 36 °C. After 45 min, the ^1H NMR spectra showed the presence of unaltered ketone **23**, with a ratio of 2/3 for the signals of the protons of the ethyl group.

3-Ethoxy-2-phenyl-1-propene 30 (X = CH_2CH_3): NMR (CCl_4) δ 1.20 (t, 3 H, J = 6.66 Hz), 3.45 (q, 2 H, J = 6.66 Hz), 4.20 (m, 2 H), 5.35 (m, 2 H), and 7.30 (m, 5 H); MS M^+ *m/e* (rel intensity) 162.2 (1.6), 119.1 (10.5), 118.1 (100), 117.1 (41.3), 105.1 (44.4), 103.1 (31.6), 91.1 (19.4), 77.1 (29.5).

1-Ethoxy-1-phenylcyclopropane 29 (X = CH_2CH_3): NMR

(CCl_4) δ 0.92 (m, 4 H), 1.15 (t, 3 H, J = 6.66 Hz), 3.45 (q, 2 H, J = 6.66 Hz), and 7.30 (m, 5 H); MS M^+ m/e (rel intensity) 162.2 (32.8), 161.1 (97.5), 133.1 (71.9), 117.1 (55.3), 115.1 (25.2), 105.1 (100.0), 91.1 (26.6), 77.1 (85.5).

3-(1′,1′,1′,3′,3′,3′-Hexafluoroisopropoxy)-2-phenyl-1-propene 30 (X = $CH(CF_3)_2$): NMR δ 4.15 (h, 1 H, J = 6 Hz), 4.72 (s, 2 H), 5.40 (m, 1 H), 5.68 (s, 1 H), and 7.35 (m, 5 H); MS M^+ m/e 284.1 (76.3), 118.1 (46.6), 117 (100), 116.0 (23.9), 115 (52.4), 105 (84.5), 104 (18), 103 (92.7), 102 (14.2), 92.1 (38.7), 91 (92.8), 77.0 (51.1).

Addition of *p*-Toluenesulfonic Acid to 2-Phenylallyl Alcohol 30. To a solution of 134 mg (1 mmol) of alcohol **30** in 2 mL of aqueous acetone (50:50) was added 190 mg (1 equiv) of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at 25 °C for 24 h and worked up anagously to alcohol **21**; the ^1H NMR spectrum of the crude residue showed unchanged allylic alcohol **30**. Again, treated by *p*-toluenesulfonic acid at 50 °C for 15 h, **30** was recovered with 90% of purity.

Kinetic procedures have been described previously.[1]

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Registry No.—**9,** 57951-69-6; **10,** 37952-37-7; **11,** 66303-65-9; **12,** 66303-66-0; **20,** 66303-67-1; **21,** 66303-68-2; **21** (X = Et), 66303-69-3; **21** (X = CH_2CF_3), 66303-70-6; **21** (X = $CH(CF_3)_2$), 66303-71-7; **22,** 54251-80-8; **29,** 29526-96-3; **29** (X = Et), 66303-72-8; **30,** 6006-81-8; **30** (X = Et), 7534-41-0; **30** (X = $CH(CF_3)_2$), 66303-73-9; cyclopropanone ethylhemiketal, 13837-45-1; cyclopropyl bromide, 4333-56-6; α-methylstyrene, 98-83-9; 3-acetoxy-2-phenylpropane, 10402-52-5; 4-phenyl-2-methylene-1-butanal, THP ether, 66303-74-0; 1-cyclopropyl-1-(2′,2′,2′,trifluoroethyl)cyclopropane, 66303-75-1.

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Micellar Acceleration of Organophosphate Hydrolysis by Hydroximinomethylpyridinium Type Surfactants

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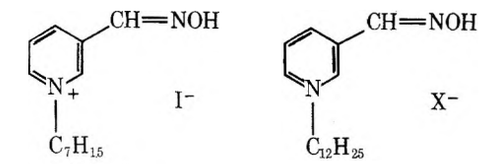
Micellar 1-*n*-dodecyl-3-(hydroximinomethyl)pyridinium salts (**2a–f**) were found to be much more effective nucleophilic reagents for the reaction with two neutral organophosphates, diethyl *p*-nitrophenyl phosphate (**3**) and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**), than nonmicellar 1-alkyl-3-(hydroximinomethyl)pyridinium salts. However, the micellar pyridinium compounds are practically ineffective in accelerating the reaction of the oximate ion with positively charged organophosphates, such as the protonated form of *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**) and *O,O*-diethoxyphosphinylthiocholine iodide (**5**). The influence of solution pH and comicellizing surfactants on the reactivity of 1-*n*-dodecyl-3-(hydroximinomethyl)pyridinium iodide (**2a**), a micellar oxime, is reported. It is concluded that the rate increase observed between micellar and nonmicellar oximes can be explained by differences in the solubility of the substrate in the micelle.

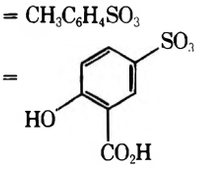
Within the past decade, a number of micelle–substrate systems have been investigated in which reactive functional groups have been incorporated into the micelle-forming molecules.[2–7] In the present work, we present our studies on the acceleration of the reaction between organophosphorus esters and an oximate ion which has been covalently bound to the backbone of a micelle. Most of the studies concerned the reaction between diethyl *p*-nitrophenyl phosphate (**3**), as the organophosphorus substrate, and 1-*n*-dodecyl-3-pyridiniumaldoxime iodide (**2a**), as the functional micellar component. However, some studies were conducted using 1-*n*-heptyl-3-hydroximinomethylpyridinium iodide (**1**). In addition, the reaction between **2a** and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**), a fully substituted

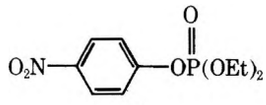


1

2a, X = I
2b, X = Cl
2c, X = Br
2d, X = CH_3SO_3
2e, X = $CH_3C_6H_4SO_3$

2f, X =





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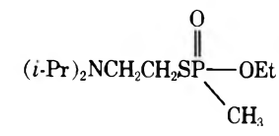

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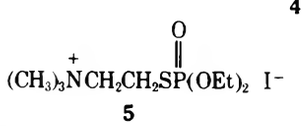

5

phosphonate which exists in the neutral, protonated, or mixture of the two forms depending upon the solution pH (pK_a of **4** = 8.6), was examined.

Selection of the oxime function as an integral part of the micelle was based on three reasons:

First, the well-documented high reactivity of the oximate ion with organophosphorus esters and the irreversibility of the reaction[8,9] make possible examination of the micellar effects in neutral or slightly alkaline pH where hydroxide ion catalysis is likely to be negligible. Under these circumstances, interpretation of the results is less ambiguous.

Second, the oxime function is present in many pharmaceutical agents used for the treatment of organophosphorus poisoning.[10] The results of this study could potentially be useful for the design of more effective organophosphorus antidotes.

Third, some anionic nucleophiles, such as hydroxamates, thiolates, and alkoxides, have significant reactivity in cationic micelles.[11] The molecular combination of an anionic nucleophile and a cationic surfactant could enhance the nucleophilicity of the anion by a "charge effect".[9]

It was found that an analogous combination, an imidazole–cationic surfactant micelle,[12] resulted in a significant increase in the hydrolysis rate of *p*-nitrophenyl esters. In these cases, it was postulated[12,13] that the imidazole anion and not the neutral imidazole moiety was the catalytic center.

The choice of a pyridinium micelle was based upon the known reactivity and therapeutic utility of pyridinium oximes. In addition, the availability of information on the micelles of dodecylpyridinium iodides[14] made them particularly attractive.

In the course of this work, Fendler et al.[15] concluded that benzophenone was solubilized in the micelle interior of hexadecylpyridinium chloride near the Stern layer in a polar environment. Similarly, the substrates used in these studies could be expected to be located in close proximity to the oximino group. The studies were conducted near the pK_a of the micellar oximes, pH 9.3.

As a standard for comparing the relative susceptibilities to nucleophilic attack of the organophosphates **3** and **4**, the hydrolysis–pH rate profile for **3** and **4**[16] in the absence of any surfactant was determined, Figure 1.

The susceptibility of **4** to nucleophilic displacement is pH dependent since the reactivity of the protonated and unprotonated forms of **4** is quite different. If the leaving group is the protonated dialkylaminoethyl mercaptan,[16] the hydrolysis rate is approximately ten times that of **3**. On the other hand, if the leaving group is the unprotonated dialkylaminoethyl mercaptan, the hydrolysis rate is approximately one-fourth that of **3**.

At pH 9.3, the half-life of **3** in the absence of detergent was 10 500 min; in 3×10^{-3} M cetyltrimethylammonium bromide (CTAB: cmc 2.5×10^{-3} M), the half-life was reduced only to

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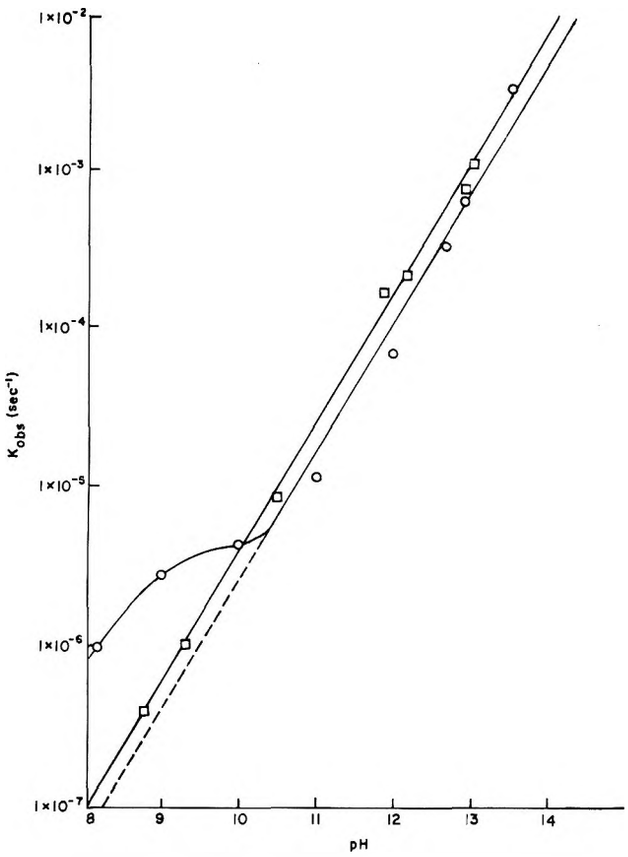

Figure 1. pH–rate profile for the hydrolysis of *p*-nitrophenyl diethyl phosphate (**3**, □) and *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (**4**, ○).

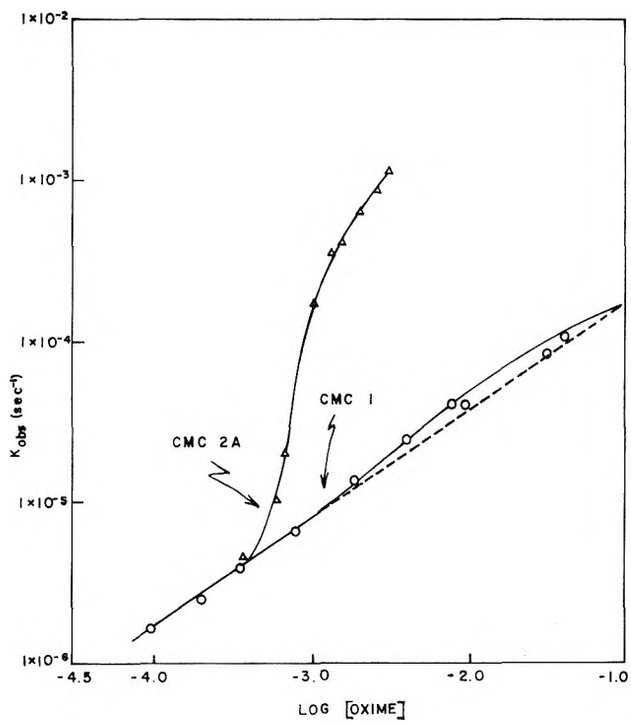

Figure 2. First-order rate constants (s^{-1}) of reaction of **3** with **1** (○) and **2a** (△) at 25 °C, pH 9.3 ($Na_2CO_3/NaHCO_3$/NaCl buffer = 0.5): cmc of **1** = 1.95×10^{-3} M; cmc of **2a** = 6.30×10^{-4} M.

8700 min. At pH 10.5, the half-life of **3** was reduced from 1200 to 1165 min by CTAB. Thus, the effect of micelles on catalysis of the hydroxide ion reaction with **3** is very small. Similarly, there was only a small increase in the hydroxide ion catalyzed hydrolysis of **4** by micelles of CTAB.

Results

Kinetics. A plot of the observed first-order rate constants (corrected for hydrolysis) for the reaction of **3** with different concentrations of **1** and **2a** in carbonate–bicarbonate buffer, pH 9.3, μ = 0.5, is shown in Figure 2. The critical micelle concentration (cmc) for the two oximes in the reaction medium were 2×10^{-3} and 6×10^{-4} M, respectively. There is a linear increase in the observed first-order rate constant with increasing concentration of **1** to approximately 4×10^{-2} M. The bimolecular rate constant, $k_2' = k_{obsd}/[1]$, over the concentration range 10^{-4}–4×10^{-2}, is $1.2 \times 10^{-2} \pm 0.0008$ M^{-1} s^{-1}. In contrast, there is a marked deviation from linearity in the concentration–rate profile for **2a.** At concentrations of **2a** less than or equal to 2×10^{-4} M, the bimolecular rate constant for **2a** is equal to that of **1** within experimental error. At a concentration of **2a** equal to 6×10^{-4} M, the bimolecular rate constant is equal to 1.5×10^{-2} M^{-1} s^{-1}. The observed rate increase is coincident with the formation of micelles as evident from the cmc (6×10^{-4} M) for **2a** in this medium. A plot of $1/(k_0 - k_{obsd})$ vs. $1/(C_d - C_{cmc})$, where k_0 is the first-order rate constant at the critical micelle concentration (C_{cmc}) and k_{obsd} is the first-order rate constant at the experimental concentration (C_d), is linear (correlation coefficient = 0.99) as predicted from mathematical micellar models.[2] Values of K/N, where K is the binding constant and N is the aggregation number, and k_m, the reaction rate constant for the reaction between **3** and **2a** in the micellar phase, calculated from the slope and intercept are 56 M^{-1} and 1.06×10^{-2} s^{-1}, respectively.

Mechanism of the Reaction. The reaction between **3** and **2a** was examined for stoichiometry and the effect of solution pH. In nonmicellar reactions, 1 mol of the organophosphorus agent is consumed per mol of oxime reacting and the reaction rate is dependent upon the oximate ion concentration.[8] The pseudo-first-order rate constant for the reaction between **2a** and **3** was determined at a concentration of **2a** well above its cmc and using a relatively low concentration of **3** ($[2a] \geq 50[3]$). In order to establish that the oxime **2a** is a true catalyst or a reagent, the reaction of **2a** with **3** was followed at a relative concentration of $[2a] \simeq 5[3]$. Following complete destruction of **3,** an additional quantity of **3** was added to the reaction mixture and the reaction rate was determined. Under these circumstances, the concentration of **2a** was greater than its cmc but lowered sufficiently such that the initial rate and the reaction rate were appreciably less than that determined in the first case. After repeating the process several more times, concentrations of **2a** were estimated from the observed second-order rate constant. Following this procedure, the stoichiometry in the micellar reaction between **2a** and **3** was demonstrated to be 1:1 and the regeneration of the oxime from the product by hydrolysis is a much slower process. The oxime **2a** is not a true catalyst but a nucleophilic reagent which deactivates the organophosphate by the formation of the corresponding oxime phosphate.

The influence of pH on the reactivity of **2a** with **3** is shown in Table I. As in the reaction of nonmicellar oximes with organophosphorus compounds,[8] the reactive species in micellar medium is the oximate ion. This thesis is substantiated by the fact that the quotient of the observed rate constant corrected for hydrolysis, k_{obsd}, and the oximate ion concentration is a constant.

Studies with More Soluble Salts and Mixed Micelles. Effect of Cosurfactants on Reaction Rates. Based on the k_m value determined for the reaction between **2a** and **3,** the maximum rate obtainable with this system corresponds to a

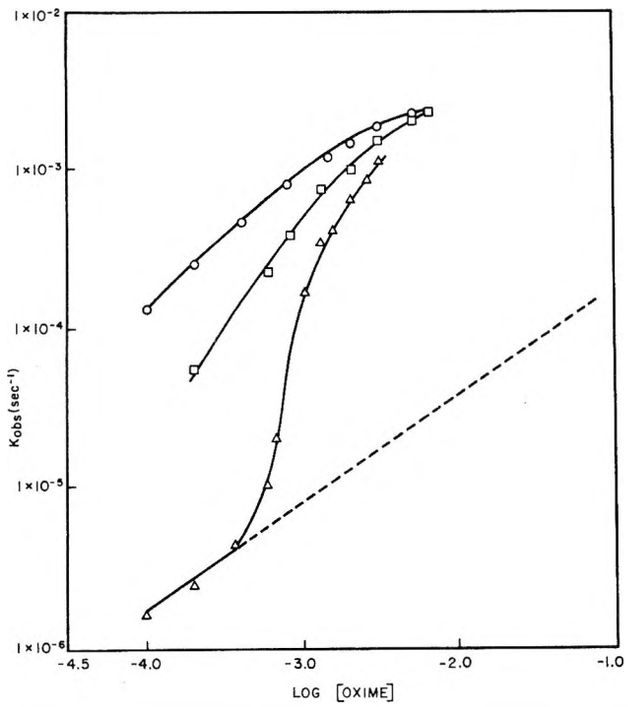

Figure 3. First-order rate constants (s^{-1}) of reaction of **3** with **2a** at 25 °C; pH 9.3 (Na_2CO_3/$NaHCO_3$/NaCl buffer = 0.5): (△) **2a**; (○) **2a** + 3×10^{-3} M CTAB; (□) **2a** + 3×10^{-3} M Brij.

reaction half-life of 1.1 min. This value is approximately an order of magnitude less than that observed with **2a.** In addition, the fraction (α) of **3** incorporated into the micellar region at the saturation concentration of **2a** (3×10^{-3} M), estimated from eq[2] 1, is 12.7%.

$$K/N = \frac{\alpha}{(1-\alpha)(C_d - C_{cmc})} \quad (1)$$

The difference between the observed rate and the maximum theoretical rate based on k_m can be attributed to the solubility of **3** in the **2a** micelle at its saturated concentration level.

Studies were conducted to determine the effect of (1) mixed micelles of 1-alkyl-3-hydroximinomethylpyridinium iodides, (2) more water soluble salts of **2a,** and (3) mixtures of **2a** with cosurfactants CTAB and polyoxyethylene 20-cetyl ether (Brij) on the reaction rate.

The effect of mixed micelles on the reaction rate of **3** is described in Table II. In mixtures of **1** and **2a,** where the mole fraction of the mixture is weighted greatly in the direction of **1,** the observed rate is close to that obtained with an equivalent concentration of only **1.** When the mole fraction is weighted greatly toward **2a,** the rate is close to that obtained with an equivalent concentration of **2a.** However, the individual contribution of each component in the micellar phase cannot be ruled out. Thus, when approximately equal concentrations of **1** and **2a** are used, the rate is equal approximately to the sum of the individual rates.

The effect of additional cosurfactants, CTAB or Brij, at a constant concentration of 3×10^{-3} M, on the first-order rate constants of the reaction of **3** with different concentrations of **2a** is shown in Figure 3. At a concentration of **2a** equal to 1×10^{-4} M, the addition of CTAB increases the rate by a factor of 82. At a concentration of **2a** equal to 1×10^{-3} M, the increase is a factor of 3 and at a concentration of 3×10^{-3} M the rate increase is less than 2. Similar qualitative data are obtained if Brij is used as the cosurfactant. The relative rate increase tends to decrease with increasing concentrations of **2a.**

A plot of the first-order rate constants for the reaction of **3** with different concentrations of various salts (**2b–f**)[17] of **2a** is shown in Figure 4. It is interesting to note that the first-order rate constants for the various salts fit very well the plot determined for **2a.** At high **2b** concentrations the curve is leveling off at a value corresponding to a half-life of approximately 1.5 min. This value approaches the half-life calculated from the maximum theoretical rate of **2a.**

Table I. Rates of Reaction of 2a (2×10^{-3} M) with 3 at Different Solution pH

pH	$(Ox^-)^a \times 10^3$	$k_{obsd} \times 10^4$	$k_{obsd}' \times 10^4$	k_{obsd}'/Ox^-
8.3	0.16	2.12	2.12	1.32
9.3	0.96	6.60	6.59	0.69
10.6	1.88	12.7	12.6	0.67
11.5	1.98	14.4	13.4	0.68
12.2	2.0	17.8	15.3	0.77

[a] Calculated from equation $(Ox^-) = [K_a/(H^+ + K_a)](Ox)_0$, where $K_a = 4.6 \times 10^{-10}$.

Table II. Half-Lives of 3 in Mixtures of 1 and 2a

[1]	[2a]	$t_{1/2}$, min
4×10^{-2}		40
	2×10^{-3}	10
4×10^{-2}	2×10^{-3}	40
4×10^{-4}		3090
	1.4×10^{-3}	28
4×10^{-4}	1.4×10^{-3}	26
9.1×10^{-4}		2238
	6×10^{-4}	2490
9.4×10^{-4}	5.9×10^{-4}	1273

Studies Using *O*-Ethyl *S*-2-Diisopropylaminoethyl Methylphosphonothiolate (4). The reaction of **2a** with **4** at various solution pH is shown in Table III. The hydrolysis pH–rate profile exhibits a pH–rate dependence similar to that observed in the reaction of **3** with **2a.** This observation is consistent with the thesis that the oximate ion is the reactive functional group in the displacement reaction. However, the relative rate of reaction between **2a** and **3** and **2a** and **4** is 4:1. This observation suggests that the micellar reaction in the case of **2a** and **4** is between **2a** and the unprotonated form of **4.** Since the reaction was examined in a pH range where **4** exists in both the protonated and unprotonated forms, it would appear that the protonated species is barred from entrance into the micelle. In support of this conclusion are the studies of the reaction between **2a** and *O,O*-diethoxyphosphinylthiocholine iodide (**5**), a model for the protonated form of **4.**

The half-life of **5** in water at pH 9.3 is 1690 min. By contrast, the half-life of **3** under the same conditions is approximately 10 000 min. The bimolecular rate constant for the reaction of a nonmicellar oxime with **3** at pH 9.3 was 0.72 M^{-1} min^{-1}. Assuming that the ratio of reactivity for the two substrates toward hydroxide ion is the same as that toward the oximate ion, the half-life of **5** in a 6×10^{-4} M solution of a nonmicellar oxime should be approximately 300 min.

The half-life of **5** in the presence of 3×10^{-3} M **2a** was found to be greater than 500 min. Thus, all the reactions occurring in a system 6×10^{-4} M with respect to oxime concentration in the aqueous phase and 24×10^{-4} M with respect to oxime concentration in the micellar phase can be accounted for by the aqueous phase reaction.

Discussion

The rate of the reaction between the oximate ion of **2a** at a concentration below its cmc and **3** is qualitatively what would be predicted from published data[10,11] for the reaction

Table III. First-Order Decomposition Rates of 4 at Different Solution pH with 3.1 ± 0.1 × 10^{-3} M 2a at 25 °C ($NaHCO_3$-Na_2CO_3 Buffer)

pH	k_{obsd}, s^{-1} × 10^4	pH	k_{obsd}, s^{-1} × 10^4
8.0	0.45	10.1	2.90
9.0	1.52	11.1	4.7
9.3	1.63		

of 1-methyl-3-hydroximinomethylpyridinium with organophosphates. The dramatic effect upon the rate coincident with the cmc and the excellent agreement of the data to a micellar model strongly support the conclusion that the increase in reactivity is due to micelles. Exclusion of the protonated form of **4** from the cationic micelle is also reasonable and the observed level of reactivity with the free base form is consistent with a micellar millieu.

The main factors affecting the rate of reaction at a given pH include the solubility of the substrate in the micelle, the association constant of the substrate with the micelle, and the geometry and aggregation number of the micelle. The latter value is important to the oximate ion concentration as well as to the association constant. Concerning the solubility of the substrate in a micelle, approximately 12% of **3** is partitioned into the micellar phase of a saturated solution of **2a.** Several experiments on the reactivity of **4** with different concentrations of **2a**[18] allow an estimate of the solubility of **4** in a saturated solution of **2a.** It was concluded that the solubility of the free base form of **4** in the micelle is similar to that of **3.** Hydrophilic organophosphorus esters may be expected to show less of an enhancement in reactivity due to micelles relative to **3.** Consistent with this hypothesis, the rate of reaction of isopropyl methylphosphonofluoridate, a very hydrophilic organophosphorus ester,[19] with micellar concentrations of **2a,** is no greater than its rate using equivalent concentrations of the nonmicellar 1-methyl-3-hydroximinomethylpyridinium iodide.[18]

The rates obtained with mixed micelles and cosurfactants are consistent with the thesis that the dominant factor in determining the rate is the solubility of the substrate in the micelle. In mixtures of **1** and **2a** which are higher in one component, the "effective cmc" of the mixture will be heavily weighted toward the richer component.[20] It is anticipated that the micelles produced from such mixtures would be very similar to the micelles of the richer component and behave as the micelle of the pure component. For mixtures in which the component compositions do not differ greatly, the micellar component will contain fractions of the two micelles in accordance with Raoults law and each micelle will contribute to the observed rate.

The results for the effect of added surfactants on the rate are consistent with the hypothesis that the reaction rate is directly proportional to the amount of substrate incorporated into the micelle and that the amount is directly proportional to the micellar volume. To a solution containing 1 × 10^{-3} M **2a,** the micellar concentration of **2a** is approximately 4 × 10^{-4} M. Addition of 3 × 10^{-3} M CTAB to the solution of **2a** provides an additional micellar concentration of approximately 5 × 10^{-4} M. Thus, the contribution of the added CTAB more than doubles the micellar volume and a corresponding increase in the reaction rate is observed. For a solution containing 3 × 10^{-3} M **2a,** the percentage increase in micellar volume upon the addition of CTAB is less and likewise its effect upon the reaction rate is decreased.

In a 3 × 10^{-2} M **2b** solution, it can be assumed that most of **3** is in the micellar phase, since using eq 1 the fraction of **3** in the micelles is approximately 63%. Assuming a density of approximately 0.8 g/mL for the 3-hydroximinomethylpyridinium micelle, the volume of a 3 × 10^{-2} M solution of **2b** is

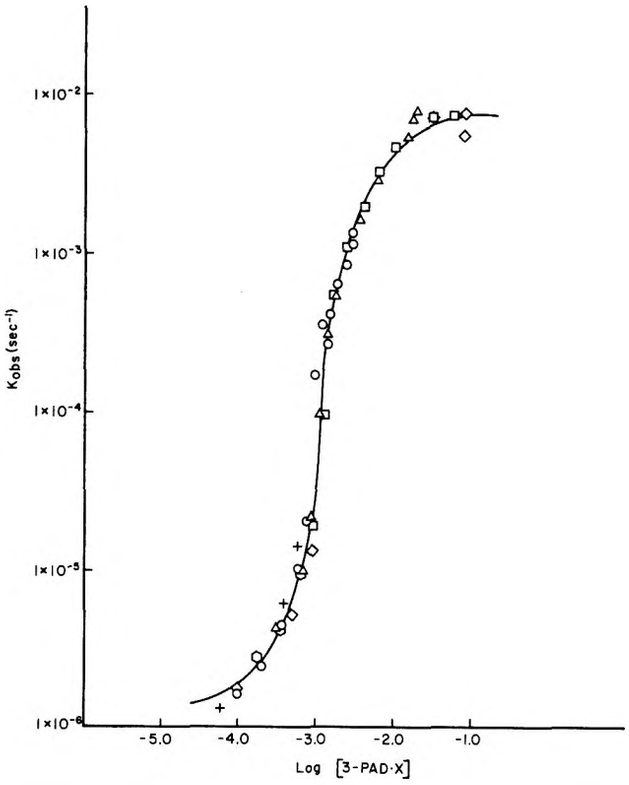

Figure 4. First-order rate constants (s^{-1}) of reaction of **3** with various 3-PAD salts at 25 °C, pH 9.3 (Na_2CO_3/$NaHCO_3$/NaCl, buffer = 0.5): (○) **2a**; (□) **2b**; (△) **2c**; (◇) **2d**; (○) **2e**; (+) **2f.**

Table IV. The pK_a of 2a at 25 °C Under Different Conditions

2a	Conditions	pK_a ± S.E.
5 × 10^{-5} M	Below cmc	9.18 ± 0.07
2 × 10^{-3} M	Above cmc	9.34 ± 0.1
5 × 10^{-5} M	3 × 10^{-3} M CTAB added[a]	9.15 ± 0.03
5 × 10^{-5} M	3 × 10^{-3} M Brij added	9.65 ± 0.15

[a] cmc of CTAB is 2.5 × 10^{-3} M.

15 mL. Therefore, the substrate concentration is 70 times greater in the micellar phase than in the aqueous phase. The first-order rate constants for the reaction between **2b** and **3** and a nonmicellar oxime and **3** are the same when the concentration of **2b** is 3 × 10^{-2} M and the concentration of the nonmicellar oxime is 1.6 M. Therefore, the reaction is 50–60 times more rapid in the micelle relative to the solution and the extent of acceleration can be wholly accounted for on the basis of the concentration effect.

Other factors which could accelerate the reaction between oximes and uncharged substrates were also considered. For example, a cationic micelle could promote ionization of the oximino hydrogen by a field effect without significant reduction in the basicity (nucleophilicity) of the anion in displacement reactions on phosphorous esters.[9] Thus, by producing more of the ionized specie without reducing its intrinsic reactivity, one could achieve a substantial rate enhancement over that observed under conditions where the field effect is not operative. The variation of the pK_a determined for **2a** in various media can be explained by a dielectric effect and an electrostatic field effect each operating in opposing directions, Table IV. With an increase in the hydrocarbon character of the medium, the ionization constant of the oximino hydrogen would be expected to decrease. However, the ionization constant would be expected to increase as the concentration of a quaternary ammonium ion increases. Thus, the normal pK_a

of 8.19 in the nonionic, hydrophobic medium provided by Brij is raised to 9.65, while in the presence of a relatively high concentration of CTAB, the pK_a is virtually unaltered. However, for concentrations of **2a** above its cmc and in the absence of CTAB, it would appear that the effect on the dielectric constant is stronger than the effect of an accumulation of the pyridinium charges. The field effect may be attenuated by a charge transfer reaction with iodide ion. Regardless, the effects, if any, are rather small and are not considered to have a large influence on the reactivity.

Experimental Section

I. Synthesis. 1-*n*-Heptyl-3-hydroximinomethylpyridinium Iodide (1). 3-Hydroximinomethylpyridine (2.44 g; 0.02 mol) and 4.61 g (0.02 mol) of *n*-heptyl iodide were mixed and heated at 120–130 °C for 0.75 h. Upon cooling to room temperature, anhydrous ether was added to the residue. Trituration in anhydrous ether gave 4.5 g (0.019 mol), 99%, of 1-*n*-heptyl-3-hydroximinomethylpyridinium iodide: mp 103–105 °C; IR (KBr) 3220, 3020, 2920, 1640, 1500. 1410, 1280, and 970 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.80 (t, 3 H), 1.2 (bs, 8 H), 1.9 (3 H), 4.6 (t, 2 H), and 7.8–9.15 (5 H).

Anal. Calcd for $C_{13}H_{21}IN_2O$: C, 44.84; H, 6.08; N, 8.05. Found: C, 44.76; H, 5.97; N, 7.94.

Using the procedure described for the preparation of **1**, 1-*n*-dodecyl-3-hydroximinomethylpyridinium iodide (**2a**) was prepared.

1-*n*-Dodecyl-3-hydroximinomethylpyridinium iodide (2a): mp 118–120 °C; IR (KBr) 3180, 2920, 2840, 1500, 1470, 1290 and 1000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.8 (t, 3 H), 1.2 (bs, 18 H), 1.9 (2 H), 4.7 (t, 2 H), and 8.9–9.6 (5 H). Anal. Calcd for $C_{18}H_{31}IN_2O$: C, 51.67; H, 7.47; N, 6.70. Found: C, 51.38; H, 7.41; N, 6.43.

The preparations of 1-*n*-dodecyl-3-hydroximinomethylpyridinium chloride (**2b**), bromide (**2c**), methane sulfonate (**2d**), *p*-toluene sulfonate (**2e**) and 5-sulfosalicylate (**2f**) have been described previously.[17]

II. Physical–Chemical Parameters. a. Solubility. Various weights of each oxime (**1** and **2a–f**) were placed in screw-capped 2 dram glass vials; 7-mL quantities of the appropriate buffer solution were added and the vials were sealed (Teflon liners). They were then shaken in a water bath thermostated at 25 °C for periods up to 7 days. Samples were taken at various intervals to ensure that equilibrium conditions had been attained.

At 25 °C, samples were filtered using a Millipore Swinnex adaptor (Millipore HAWD01300 0.45 μm filter) and diluted in a vehicle of ethanol/pH 9.3 carbonate buffer[21] (50:50 v/v) to approximately $0.1–1 \times 10^{-4}$ M. The absorbance of the resulting solutions at 290 or 295 nm was measured and the solubilities were calculated based on the respective molar absorptivities: **1**, $\epsilon_{295} = 1.21 \times 10^4$ M^{-1} cm^{-1}; **2a**, $\epsilon_{295} = 1.29 \times 10^4$ M^{-1} cm^{-1}; **2b**, $\epsilon_{290} = 1.17 \times 10^4$ M^{-1} cm^{-1}; **2c**, $\epsilon_{290} = 1.22 \times 10^4$ M^{-1} cm^{-1}; **2d**, $\epsilon_{290} = 1.07 \times 10^4$ M^{-1} cm^{-1}; **2e**, $\epsilon_{290} = 1.03 \times 10^4$ M^{-1} cm^{-1}; and **2f**, $\epsilon_{295} = 1.54 \times 10^4$ M^{-1} cm^{-1}.

b. Critical Micelle Concentration (cmc). A concentrated solution of each oxime (**1** and **2a**) in buffer[21] was prepared, assayed, and serially diluted to produce a range of concentrations. The solutions were equilibrated at 25 ± 0.2 °C. Using a Hitachi Perkin-Elmer MPF-2A spectrophotofluorimeter to excite the solutions at a wavelength of 410 nm, the intensity of the Raman peak of water occurring at 478 nm was recorded. This intensity was plotted against oxime concentration and the inflection point in the curve determined the critical micelle concentration (cmc). The critical micelle concentration of **1** and **2a** was 1.95×10^{-3} and 6.30×10^{-4} M, respectively.

c. pK_a Determination of 1-*n*-Dodecyl-3-hydroximinomethylpyridinium Iodide (2a). The pK_a of 1-*n*-dodecyl-3-hydroximinomethylpyridinium iodide (**2a**) above and below the critical micelle concentration (cmc) and in the presence of 3×10^{-3} M cetyltrimethylammonium bromide (CTAB) and Brij was determined spectrophotometrically. Carbonate–bicarbonate buffers ranging in pH from 5.8 to 12.8 were prepared and used to prepare the following solutions: (1) 5×10^{-5} M **2a**, below cmc; (2) 2×10^{-3} M **2a**, above cmc; (4) 5×10^{-5} M **2a** in 3×10^{-3} M CTAB; and (4) 5×10^{-5} M **2a** in 3×10^{-3} M Brij.

The absorption spectra of these solutions were determined from 220 to 450 nm. The absorbance at 295 nm was plotted against the pH of the buffer solutions. Sigmoidal curves were obtained and the pK_a values were calculated based on three determinations around the point of half neutralization using the equation

$$pK_a = pH_{obsd} + \log \frac{[A_{max} - A_{obsd}]}{[A_{obsd} - A_{min}]}$$

where A_{max}, A_{min}, and A_{obsd} are the absorbance values for the dissociated, undissociated, and the partly dissociated (at pH_{obsd}) solutions of **2a**.

III. Chemical Kinetics. a. Kinetic Studies using *p*-Nitrophenyl Diethyl Phosphate (3). All reactions were carried out in a carbonate buffer system (prepared using 0.1 M sodium carbonate and 0.1 M sodium bicarbonate) of ionic strength 0.5 (added sodium chloride).[21] The concentration of **3** was 3.63×10^{-5} M. The formation of the *p*-nitrophenolate ion was followed spectrophotometrically at 400 nm using a Cary 14 spectrophotometer equipped with an automatic sampling accessory thermostated at 25 ± 0.2 °C.

The reactions were started by adding 25 μL of a 1% v/v solution in dioxane of the phosphate ester to 25 mL of oxime solution equilibrated for 1 h at the temperature investigated.

The reactions were followed for a minimum of 3 half-lives and always obeyed first-order kinetics. Rate constants were calculated from half-lives obtained from semilogarithmic plots of $A_\infty - A_t$ against time (A_∞ is the absorbance at the end point of the reaction and A_t is the absorbance at any time t).

b. Kinetic Studies Using *O*-Ethyl *S*-2-Diisopropylaminoethyl Methylphosphonothiolate (4). Solutions containing approximately 0.1 M Na_2CO_3, 0.1 M $NaHCO_3$, 0.2 M NaCl, 3×10^{-3} M **2a**, and 10^{-3} M CTAB were prepared by dissolving the appropriate quantities of materials in about 45 mL of distilled water. The pHs of the solutions were adjusted with concentrated NaOH or HCl solutions and the volumes raised to 50 mL. The solutions were placed in a water bath at 25 °C for about 15 min and 5 μL of **4** (ca. 86%) was added. The solutions were vigorously shaken for about 10 s and returned to the water bath. Aliquots were removed by a rapid-fill 5-mL syringe and put into 5 mL of CCl_4 and shaken 5 s; on separation the bottom layer was collected. This CCl_4 layer was placed in a 10-mL volumetric flask containing a small amount of anhydrous K_2CO_3 to absorb any water present in the CCl_4 solution. The **4** was assayed by VPC: 10 μL; 5% UCW-98 on W.H.P. 100–120 mesh; 2 min at 200 °C; 16 in./min up to 270 °C; 270 °C for 2 min-He 50 psi; 3 3.6 min; disulfide 6.5 min.

The peak heights of **4** were linear with concentration and referenced to a 1000-ng sample. Less than 1 ng could be detected. The **4** was extracted into the CCl_4 with close to 100% efficiency.

c. Kinetic Studies Using (2-Mercaptoethyl)trimethylammonium Iodide *O,O*-Diethylphosphorothioate; Phospholine Iodide (5). All reactions were carried out in a carbonate buffer system (prepared by use of 0.1 M sodium carbonate and 0.1 M sodium bicarbonate) of ionic strength 0.5 (added sodium chloride).[21] The concentration of **5** was 7.38×10^{-5} M.

The hydrolysis product of **5**, thiocholine, can react with 5,5-dithiobis(2-nitrobenzoate) (DTNB) to produce a yellow colored anion. The rate of this color formation may be measured at 412 nm.[22] Because phospholine iodide is moderately stable in neutral and acidic solution, the reaction could be quenched at time intervals and immediately put into 4 mL of phosphate buffer, pH 7. DTNB (0.2 mL) was added to each sample just before recording the absorbance at 412 nm. The A_∞ was calculated from the initial concentration of phospholine iodide using the known molar absorptivity of 1.35×10^4 M^{-1} cm^{-1}. Only the initial slopes of semilogarithmic plots of $A_\infty - A_t$ against time were taken to calculate the reaction rate constants.

In the case where **2a** was present in the solution, the reaction solution was diluted using a 4:1 water–ethanol mixture.

Registry No.—**1**, 66290-87-7; **2a**, 66290-86-6; **2b**, 66290-85-5; **2c**, 66290-84-4; **2d**, 66290-91-3; **2e**, 66290-90-2; **2f**, 66290-89-9; **3**, 311-45-5; **4**, 50782-69-9; **5**, 513-10-0; 3-pyridinealdoxime, 1193-92-6; heptyl iodide, 4282-40-0.

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The Intermediate from the Triphenylphosphine–Tetrachloromethane–Alcohol Reaction: Relative Rates of Intermediate Formation, Kinetics, and Mechanism of Intermediate Decomposition

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The rate of formation of the phosphorylated intermediate formed by reacting triphenylphosphine, carbon tetrachloride, and an alcohol is only slightly influenced by steric effects. The relative rates of intermediate formation are primary > secondary > neopentyl. The relative rates of intermediate decomposition follow the order primary > secondary > neopentyl. Thus neopentyl alcohol reacted with the phosphorylating agent at room temperature to form an intermediate without concomitant decomposition to neopentyl chloride. The structure of the intermediate was elucidated by ^1H NMR and ^{31}P decoupling. Rates of decomposition to the respective alkyl chlorides of the phosphorylated intermediates formed from neopentyl alcohol and from 1,1-dideuterio-2,2-dimethylpropanol were run at various temperatures. Clean first-order kinetics were obtained as well as the energetics for the decomposition reaction. A small positive α hydrogen kinetic isotope effect was obtained and the various mechanisms of intermediate decomposition to chloride product are discussed in terms of rate constants, the energetics, and the isotope effects.

The reaction of triphenylphosphine, carbon tetrachloride, and alcohols gives rise to an elegant method for the synthesis of primary and secondary alkyl chlorides.

$$(C_6H_5)_3P + CCl_4 + ROH \rightarrow RCl + (C_6H_5)_3PO + CHCl_3 \quad (1)$$

In 1966, the preparation of acyl chlorides[1] by the reaction of a carboxylic acid with triphenylphosphine and carbon tetrachloride was extended to the preparation of alkyl chlorides from alcohols, triphenylphosphine, and carbon tetrachloride.[2]

Similarly, tri-*n*-octylphosphine and carbon tetrachloride were used to convert primary and secondary alcohols to the corresponding chlorides with inversion of configuration; the production of tertiary chlorides gave very poor yields, possibly due to elimination being the primary reaction.[3] The use of carbon tetrabromide, trialkyl- or triarylphosphines, and primary or secondary alcohols led to alkyl bromides. Again, inversion of configuration seemed to predominate in this synthetic procedure.[3] The ease with which chlorides were formed with inversion of configuration was explored by R. G. Weiss and E. I. Snyder in several papers.[4a-c]

The various pathways for intermediate formation have been investigated by Appel and have been summarized in an excellent review article by the same author.[5] The overall mechanism of the reaction is presumed to proceed via eq 2.[5]

$$(C_6H_5)_3P + CCl_4 \rightarrow [(C_6H_5)_3PCl]^+CCl_3^-$$

$$[(C_6H_5)_3PCl]^+CCl_3^- + ROH \rightarrow [(C_6H_5)_3POR]^+Cl^- + HCCl_3$$

$$[(C_6H_5)_3POR]^+Cl^- \rightarrow RCl + (C_6H_5)_3PO \quad (2)$$

In more detail, the formation of the intermediate can be formulated in part as follows:[5]

$$(C_6H_5)_3\overset{\delta+}{P}\cdots Cl\cdots\overset{\delta-}{C}Cl_3 \rightarrow [(C_6H_5)_3POR]^+Cl^- + HCCl_3 \quad (3)$$

(R–O–H)

Appel[5] has also described other minor routes to the phosphorylated intermediate involving $(C_6H_5)_3PCl_2$ and $(C_6H_5)_3PCCl_2$, but they will not be discussed in this manuscript.

There are a number of gaps in this mechanistic picture that need to be filled and clarified: First, it must be noted that nowhere is there any mention of the relative rates of formation and decomposition of the intermediate. Second, it will be noted that the intermediate has been described as an ion pair with a phosphorus–oxygen–carbon bond. At present there is no hard evidence for this assumption. Third, it must be emphasized that although the intermediate has been described as undergoing a first-order decomposition to product, there is no concrete evidence to date that this implied kinetic order is a reality.

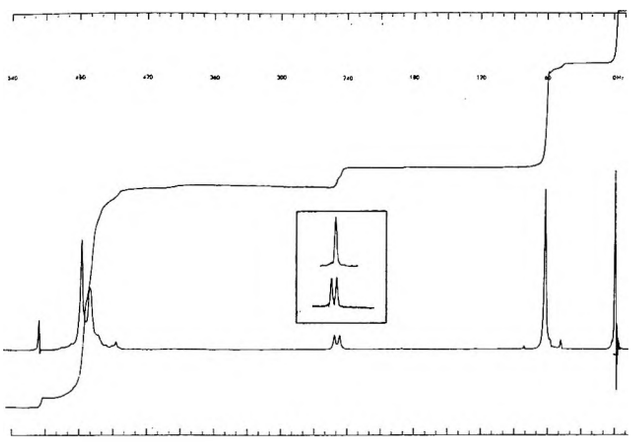
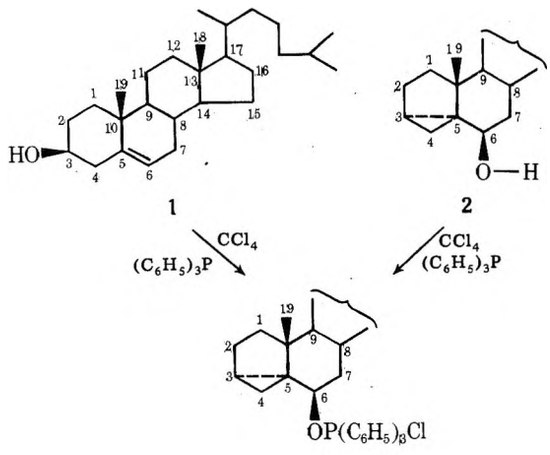


Figure 1. The ^1H NMR spectrum of compound **6** in $CDCl_3$–CCl_4. The inset shows the CH_2–O–^{31}P doublet and its collapse to a singlet peak upon ^{31}P irradiation.

First, we propose to show that for sterically unhindered primary alcohols the rate of intermediate decomposition to alkyl chloride is faster than the rate of intermediate formation; for secondary alcohols the rate of intermediate decomposition is slowed much more dramatically than the rate of intermediate formation, and for the neopentyl alcohol system, the rate of intermediate formation is many times faster than the rate of intermediate decomposition. Second, we will show that the intermediate contains a phosphorus–oxygen–carbon bond. Third, we have run decomposition kinetics on the phosphorylated neopentyl intermediate to neopentyl chloride and have verified that indeed the decomposition is first order. Finally, we have run decomposition kinetics on 1,1-dideuterio-2,2-dimethylpropanol and obtained an α hydrogen kinetic isotope effect showing that the decomposition proceeds via an intramolecular S_N2 substitution.[6]

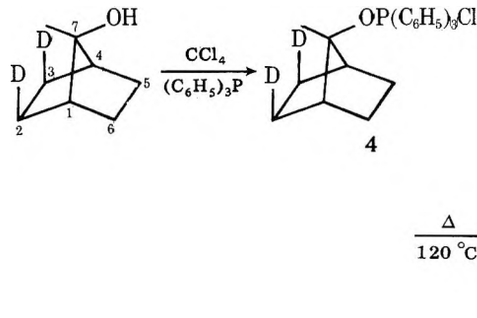
Results

The isolation of a crude intermediate has been noted by Aneja, Davies, and Knaggs[7] where some intermediate phosphorylated derivative (**3**) was obtained both from the reaction of cholesterol (**1**) and from isocholesterol (**2**). The "proof" of



1 2 3

structure of **3** resided in the fact that the chemical shift for the 19-CH_3 was at δ 0.4 suggesting spacial proximity to the substituent at C-6. The only other known case was that of Weiss and Snyder[4b] who had shown that a crude preparation of *anti*-**4** could be isolated and decomposed thermally (with approximate first-order kinetics) to *syn*-**5**. It is well known that reactions in the 7-substituted norbornyl system proceed slowly with inversion.[8] So, in order to duplicate this type of



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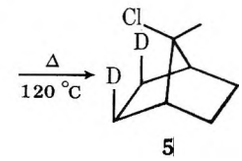

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system in the acyclic series, neopentyl alcohol was chosen as a model compound since displacement with inversion on neopentyl-substituted compounds also proceeded slowly. When neopentyl alcohol was treated with triphenylphosphine and carbon tetrachloride, it was observed that the hydroxyl proton area decreased and at the same time underwent a shift to lower field. For example, at the beginning of the reaction, the hydroxyl proton appeared at δ 2.97, and after 513 min the last vestiges of the **OH** appeared at δ 6.77. At the same time the **OH** was shifting and decreasing in area, the CH_2O (δ 3.32) area of the original alcohol was decreasing and a new peak appeared as a doublet ($J \simeq 4.3$ Hz) at δ 4.17. The increase in area of the new peak was equal to the decrease in area of the CH_2O peak of the alcohol. The ^1H NMR data were consistent with compound **6**. Since it was known for trineopentyl phosphate (**7**) that the J_{CH_2OP} coupling constant was 5.24 Hz,[9] it was presumed that the doublet arose from a ^{31}P coupling. That this was indeed a ^{31}P coupling was further substantiated by ^{31}P irradiation of the intermediate which resulted in collapse of the doublet to a singlet. (See Figure 1.) Thermal treatment of intermediate **6** led to formation of neopentyl chloride.

$$(CH_3)_3CCH_2OH \xrightarrow[CCl_4]{(C_6H_5)_3P} (CH_3)_3CCH_2OP(C_6H_5)_3Cl$$

6

$J_{CH_2OP} = 4.3$ Hz

$[(CH_3)_3CCH_2O-]_3P{=}O$

7

$J_{CH_2OP} = 5.24$ Hz

We were able to follow this, not only by product isolation but by ^1H NMR spectroscopy. Thus, the CH_2O doublet of the intermediate (δ 4.17) collapsed to a singlet (CH_2Cl, δ 3.27) of the product. We also noted that as the intermediate *tert*-butyl group decreased in area there was a concomitant increase in the area of the product *tert*-butyl group. Since the reaction involving intermediate formation is a result of front-side attack (see eq 3), we assumed that the rate of intermediate formation should be essentially free of any steric requirements. To test this hypothesis, the relative rates of disappearance of benzyl alcohol vs. neopentyl alcohol were determined by ^1H NMR spectroscopy. In the case of benzyl alcohol no intermediate was detected by ^1H NMR, so it was assumed that the rate of intermediate decomposition was much faster than its rate of formation. Thus by ^1H NMR we were able to observe benzyl alcohol, benzyl chloride, neopentyl alcohol, and the neopentyl intermediate (**6**). Furthermore, by assuming that the alcohols were consumed unimolecularly, it was determined that the relative rate of benzyl alcohol disappearance to neopentyl alcohol disappearance was about 7.4/1. The data did range in relative rates from a high of 8.5 to a low of 6.5. However, it does support the front-side attack hypothesis (eq 3) since it is known that for back-side displacement reactions the relative rate of $PhCH_2X$/neopentyl-X is about 30 000 000/1.0.[10] The above compounds were chosen at opposite extremes of nucleophilic displacement reactions to emphasize that to

Table I. Material Balance for Competition Kinetics of 3-Methyl-1-butanol vs. 1-Pentanol[a]

Time, min	1-Pentanol A[c]	Isoamyl OH B[c]	1-Chloropentane[c]	Isoamyl Cl[c]	Int. A[b]	Int. B[b]
15	1.60	1.75	0.09	0.03	0.51	0.42
75	1.45	1.67	0.45	0.15	0.30	0.38
138	0.82	1.09	0.82	0.35	0.56	0.76
210	0.31	0.57	1.57	0.63	0.32	1.00
300	0.10	0.25	1.80	0.75	0.30	1.20
390	0.02	0.02	1.99	1.17	0.19	1.01
T_∞	0.02	0.02	2.00	2.01	0.18	0.17
58	1.62	1.80	0.34	0.17	0.24	0.23
127	0.81	1.11	0.77	0.38	0.62	0.71
195	0.45	0.70	1.56	0.57	0.19	0.93
268	0.33	0.60	1.61	0.80	0.26	0.80
376	0.05	0.07	1.88	1.13	0.27	1.00
T_∞	0.01	0.02	1.99	2.00	0.20	0.18

[a] Run in excess chlorinating agent. Initial alcohols: 2.20 mmol of each alcohol. [b] Intermediates are assumed for material balance of original alcohol minus alcohol and chloride at time t as the amount of phosphate intermediate which has not decomposed. [c] Units are millimoles.

Table II. Material Balance for Competitive Kinetics of 1-Pentanol vs. 2-Pentanol[a]

Time, min	1-Pentanol A[c]	2-Pentanol B[c]	1-Chloropentane[c]	2-Chloropentane[c]	Int. A[b]	Int. B[b]
10	1.80	2.00			0.40	0.20
72	1.48	1.84	0.43	0.10	0.29	0.26
135	1.12	1.60	0.81	0.20	0.27	0.40
210	0.73	1.32	1.36	0.32	0.11	0.56
278	0.15	0.81	1.94	0.42	0.11	0.97
343	0.02	0.48	2.00	0.52	0.18	1.20
T_∞	0.02	0.02	2.01	1.98	0.17	0.20
15	1.60	1.90			0.60	0.30
150	0.85	1.45	0.90	0.22	0.45	0.53
230	0.36	1.00	1.38	0.32	0.46	0.88
290	0.17	0.69	1.74	0.43	0.29	1.08
T_∞	0.02	0.02	1.99	1.98	0.19	0.20

[a] Run with excess chlorinating agent. Initial alcohols: 2.20 mmol of each alcohol. [b] Intermediates are assumed for material balance of original alcohol minus alcohol and chloride at time t as the amount of phosphate intermediate which has not decomposed. [c] Units are mmoles.

a large extent intermediate formation is *not* sterically controlled. To determine the possibility of intermediate formation in simple, acyclic systems, 1-pentanol vs. 2-pentanol and 1-pentanol vs. 3-methyl-1-butanol (isoamyl alcohol) were reacted competitively with triphenylphosphine and carbon tetrachloride. If an intermediate were being formed, this would be reflected by the relative rates of 1-pentanol vs. the other two alcohols showing only a small difference in rates, presumably due to small secondary effects of steric hindrance.

Competitive kinetics for the disappearance of alcohol or appearance of alkyl chloride by GLC can be misleading in this type of system. The reason for this caveat lies in the fact that the decomposition of intermediate has a high energy of activation (this will be discussed later) so that volatilization of the sample in the injection port of the chromatograph caused an increase of intermediate decomposition to alkyl chloride. In order to minimize the results due to intermediate decomposition, thermostated samples consisting of alcohol, triphenylphosphine, chloroform-*d*, and tetrachloromethane were removed from time to time and connected to a high vacuum system to trap all the alkyl chloride, $CDCl_3$, CCl_4, and much of the unreacted alcohol. As described in the Experimental Section, the alcohol and alkyl chlorides were determined (quantitatively) by GLC using an internal standard. Essentially *all* the volatile alkyl chloride (plus a large amount of alcohol) was removed under vacuum leaving a small amount of the less volatile unreacted alcohol and the intermediate. This residue was analyzed separately by GLC using an internal standard. Thus the amount of alcohol that had reacted was a reliable value since all the CCl_4 which could form intermediate was removed under vacuum; there is of course an inherent source of error overestimating the amount of alkyl chloride formed and underestimating the amount of intermediate present in the reaction mixture at any time. This of course arises from the amount of intermediate which decomposes to alkyl chloride. Nevertheless, the material balance was relatively reliable and consistent in almost all our experiments and at no time was the material balance over 20% and was generally well within the 10% mark. Consistently, it was noted that 1-pentanol reacted only 1.4 times as fast as isoamyl alcohol and only 2.2 times as rapidly as 2-pentanol with both excess chlorinating agent and excess alcohol. These relative rates were fully consistent with the formation of a discrete intermediate. However, as shown in Tables I and II, which summarize the material balance of 1-pentanol vs. isoamyl alcohol (Table I) and 1-pentanol vs. 2-pentanol (Table II), the intermediate from 1-pentanol increased only very slightly during the course of the reaction, but the intermediate from both isoamyl alcohol and 2-pentanol increased markedly in the first part of the reaction and then decreased. If the case of isoamyl alcohol were taken and it was assumed that as much as 0.2 mmol of product and/or intermediate could not be found (Table I, top portion), it would be noted that at 300 min there was 1.2 mmol of isoamyl intermediate. Even with an error of 0.2 mmol, there was still at least 1.0 mmol of intermediate

Table III. Rates and Kinetic Isotope Effects for Decomposition of Intermediates from Neopentyl Alcohol and 1,1-Dideuterio-2,2-dimethylpropanol (10)

Temp, °C	$k_H \times 10^5$, s^{-1} [a]	$k_D \times 10^5$, s^{-1}	k_H/k_D
40	1.40	1.30	1.077
49.8	5.57	5.02	1.109
59.9	20	17	1.176
70.3	66	63	1.047
		k_H/k_D (av)	1.102 ± 0.055

[a] Average of two kinetic runs at each temperature.

formed. This value was too large to ignore and graphically illustrated the intermediate formation.

It was quite apparent from our competitive studies that the slow step in alkyl chloride formation was due to rate of intermediate decomposition rather than rate of intermediate formation for secondary alcohols and neopentyl alcohol. Sterically unhindered primary alcohols not only formed intermediate rapidly but the intermediate, in turn, quickly decomposed to primary alkyl chloride. From Tables I and II it will be noted that even with a large excess of 1-pentanol in the early part of the reaction (10 to 150 min) there is always much more 1-chloropentane formed than intermediate present, strongly suggesting that the rate of intermediate decomposition of unhindered primary alcohol is more rapid than the rate of intermediate formation. This is certainly true for benzyl alcohol.

Once we had established the relative rates of intermediate formation and decomposition of various substrates, it became of interest for us to look at the rate of intermediate decomposition more critically in order to absolutely ascertain the order of the decomposition reaction, the energetics of the decomposition, and the kinetic isotope effect for the rate of decomposition. These results are of utmost importance when evaluating any proposed decomposition mechanism. Any mechanism that is proposed must be consistent with the stereochemistry of the reaction, the kinetics, the energetics, and the isotope effect. We needed an alcohol which would form intermediate much more rapidly than the corresponding intermediate would decompose to alkyl chloride; in addition we needed to know the stereochemical course of intermediate decomposition of this specific alcohol. The alcohol of choice was neopentyl alcohol (2,2-dimethylpropanol). We had found from competitive kinetics that we could readily form the neopentyl intermediate at ambient temperatures with insignificant intermediate decomposition; in addition it is known that the reaction of (*R*)-1-deuterio-2,2-dimethylpropanol (**8**) with tetrachloromethane and triphenylphosphine proceeds with greater than 85% inversion to form (*S*)-1-deuterio-2,2-dimethylpropyl chloride (**9**).[4c]

$$(R)\text{-}(CH_3)_3CCHDOH + CCl_4 + (C_6H_5)_3P \rightarrow (S)\text{-}(CH_3)_3CCDHCl$$

8 **9**

Not only did we need a system that would give reliable kinetics, but in addition we needed a system whereby we could study the kinetic isotope of an α,α-dideuterated system in order to get some conception of the amount of bond making and bond breaking of the intermediate to form the deuterated neopentyl chloride. To this end we synthesized 1,1-dideuterio-2,2-dimethylpropanol (**10**) via the $LiAlD_4$ reduction of methyl trimethylacetate (methyl pivalate). The alcohol obtained (**10**) had 1.95 D per molecule.

Table IV. Energetics for Decomposition of Intermediates from Neopentyl Alcohol and 1,1-Dideuterio-2,2-dimethylpropanol (10)

Compd	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
$(CH_3)_3CCH_2OP(C_6H_5)_3Cl$	27.14 ± 0.34	4.05 ± 0.02
$(CH_3)_3CCD_2OP(C_6H_5)_3Cl$	27.18 ± 0.34	3.98 ± 0.02

$$(CH_3)_3CCO_2CH_3 + LiAlD_4 \rightarrow \rightarrow (CH_3)_3CCD_2OH$$

10

We were able to monitor disappearance of neopentyl alcohol, appearance of intermediate, and appearance of neopentyl chloride by ^1H NMR spectroscopy. However, we did not have the CH_2O peak for the dideuterated derivative so we used the difference in the chemical shift of the *tert*-butyl group in the neopentyl series to monitor the reaction.

$(\mathbf{CH_3})_3CCH_2OH$ δ 0.875

$(\mathbf{CH_3})_3CCH_2OP(C_6H_5)_3Cl$ δ 1.033

$(\mathbf{CH_3})_3CCH_2Cl$ δ 0.967

In addition we were able to obtain kinetics by ^1H NMR spectroscopy by measuring relative peak heights of intermediate and product.

Clean first-order kinetics were obtained up to and even over three half-lives of reaction for both neopentyl alcohol and the deuterated alcohol, compound **10**. We ran the kinetics simultaneously on the deuterated and nondeuterated neopentyl alcohols so that even if it should have turned out that our kinetic method may not have been absolute our relative kinetic isotope effect would have been valid. Our fears were ungrounded, however, and we obtained good first-order kinetics with correlation coefficients ranging from 0.997 to 0.999. In addition we were able to get correlation coefficients of 0.9998 on our Arrhenius plots. The kinetic data are summarized in Table III. It is possible that the values of the individual rate constants may not be accurate to the precision listed in the table. However, the relative values of the kinetic isotope effect should be reliable to the significant digits shown in the fourth column of Table III. It will be noted that the average experimental kinetic isotope effect (k_H/k_D) is 1.102 with small but abnormal temperature dependence. If one looks at the effect of just one deuterium, the kinetic isotope effect is 1.050. Indeed, this is a *very small* kinetic isotope effect. It can be seen in Table IV that the energies of activation for both neopentyl alcohol and compound **10** are essentially equal, the only small difference really residing in a slightly larger $\Delta S^{\ddagger}$ for the hydrogen isomer.

Discussion

We can now briefly summarize both our results and those of other authors in the preparation of alkyl chlorides by reaction of an alcohol with triphenylphosphine and carbon tetrachloride:

(i) Reactions generally proceed in two steps as in (a) and (b)

$$ROH + (C_6H_5)_3P + CCl_4 \rightarrow [(C_6H_5)_3\underset{\displaystyle Cl}{\overset{|}{P}}OR] + CHCl_3 \quad (a)$$

$$(C_6H_5)_3\underset{\displaystyle Cl}{\overset{|}{P}}OR \rightarrow RCl + (C_6H_5)_3PO \quad (b)$$

(ii) In the case of primary alcohols (sterically unhindered) step (a) is probably slower than (b) but for secondary alcohols and neopentyl alcohol step (a) is faster than step (b).

(iii) There is hard evidence for an intermediate, in particular, $(CH_3)_3CCH_2OP(C_6H_5)_3Cl$.

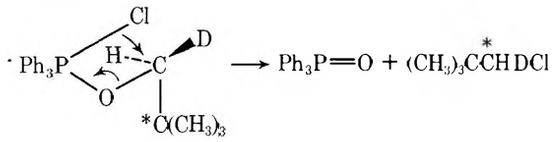
(iv) The rate of decomposition of the above intermediate follows clean first-order kinetics with an energy of activation of about 27 kcal/mol and an entropy of activation of about +4 eu.

(v) A greater than 85% inversion of configuration has been noted for the neopentyl system;[4c] thus greater than 92% back-side attack must be assumed for the thermal decomposition of $(CH_3)_3CCH_2OP(C_6H_5)_3Cl$ to $(CH_3)_3CCH_2Cl$.

(vi) The very small isotope effect per deuterium ($k_H/k_D \sim 1.050$) indicates a nearly balanced bond-making, bond-breaking process.

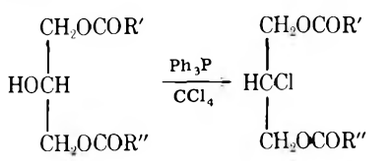
From a purely operational point of view the thermal decomposition of $(CH_3)_3CCH_2OP(C_6H_5)_3Cl$ to $(CH_3)_3CCH_2Cl$ must be an intramolecular S_N2 process with very little ion-pair character.[6] We can state this with complete confidence because of the large amount of inversion and the very small kinetic isotope effect. The kinetic isotope effect argument that this process has a nearly balanced bond making and bond breaking in what is usually known as an S_N2 process proceeds as follows.[11] From a theoretical point of view, the hydrogen kinetic isotope effects (KIE) depend on the symmetry properties of the transition state. The very small KIE that we experienced could be contributed totally from the temperature independent factor (TIF), namely the isotopic rate ratio resulting from the reaction coordinate, $\nu_H^{\ddagger}/\nu_D^{\ddagger}$, the variation of KIE over the limited temperature range could be explained as the result of the EXC (excitation) term. This argument fits our data rather well, since only a small isotope effect in entropy of activation can be accounted for from our experimental results. The zero-point energy difference (ZPE) is negligible; the small contribution must be from EXC assuming that for an intramolecular S_N2 the contribution from the moment of inertia change is small.

There have been a couple of interesting approaches toward the mechanism of intermediate decomposition. Under the assumption that the intermediate is a trigonal bipyramid, there is the so-called four-center mechanism whereby P–Cl bond breaking precedes somewhat C–O bond cleavage in a very tight ion pair.[4b]

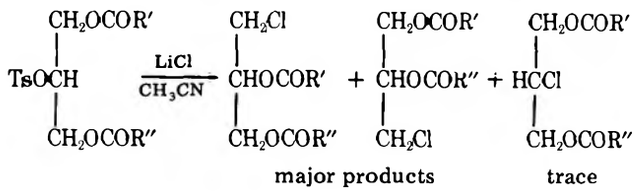


Ph ≡ C_6H_5

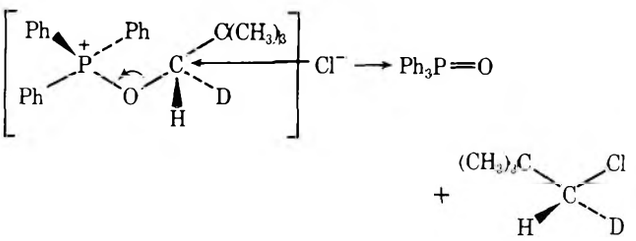
With sufficient C–O bond cleavage the above mechanism would require a measurable retention of configuration as has been noted by both Snyder[4b] and Mosher.[12] The nonconcerted P–Cl, C–O bond cleavage postulated by Snyder[4b] in the four-centered mechanism has been disputed by Aneja, Davies, and Knaggs.[13] These authors reacted acylglycerols with triphenylphosphine and tetrachloromethane and obtained only configurational inversion and no rearrangement due to acyloxy neighboring group participation.



If the corresponding *p*-toluene sulfonate (tosylate ≡ Ts) was reacted with lithium chloride in acetonitrile then both 1- and 3-substituted chlorodeoxydiacylglycerols were the major products resulting from acyloxy neighboring group participation.



Since *no* neighboring group was observed with $Ph_3P + CCl_4$, these authors disputed the prior P–Cl bond cleavage postulated by Weiss and Snyder.[4b] This argument is not valid since it is the extent of C–O cleavage which is involved in neighboring group participation of the acyloxy group *not* the amount of P–Cl cleavage. If the intermediate is written as an



ion pair with the phosphorus tetrahedrally coordinated[5] then the inversion of configuration and the energetics of the thermal decomposition are readily rationalized by the above mechanism.

The energetics observed for this type of process is not unreasonable. Thus, it is known that the nucleophilic substitution of neopentyl bromide with ethoxide ion in ethanol has an energy of activation of 26.2 kcal/mol.[14] This is quite close to our observed value of 27.1 kcal/mol and presumably 5–6 kcal/mol of this activation energy is steric in origin due to the bulk of the neopentyl group. The observed entropy of activation of +4 eu is fairly close to zero and is consistent with the above picture of an intramolecular S_N2 reaction. Indeed we would anticipate that the entropy of activation would increase markedly as the amount of C–O bond rupture increased; the above mechanism is therefore in accordance with the small isotope effect and the observed stereochemistry.

There are some flaws in the above picture; we have artificially placed the nucleophilic chloride adjacent to the electrophilic carbon and separated the positive phosphorus from the negative chloride in order to satisfy our steric requirements for a reaction of greater than 92% back-side attack. Such a charge separation is energetically unreasonable. If, however, we postulate that the ion pair is *not* a lone entity but is instead structured as a cluster of ion pairs in two and/or three dimensions wherein a positive phosphorus in one ion pair is in part electrically neutralized by a negative chloride from (an) other ion pair(s), then the ion-pair electrostatic picture becomes more reasonable. Rationalization for this model is remotely justified by noting that even interaction of *R*–*S* enantiomers is sufficiently strong so that the ^1H NMR of a racemic mixture can differ measurably from that of the pure enantiomer in an achiral solvent.[15]

Another flaw in the above model resides in the fact that an external nucleophile such as cyanide ion was unable to compete with chloride ion in the reaction of 2-phenylethanol, with triphenylphosphine–carbon tetrachloride in dimethyl sulfoxide.[4c] Yet 2-phenylethyl tosylate in dimethyl sulfoxide gave better than 19/1 2-phenylethyl cyanide to 2-phenylethyl chloride starting with equimolar amounts of cyanide and chloride ion.[4c] This could, of course, be a result of a very tight ion pair, but operationally it becomes difficult to distinguish between the tight ion pair with that of a covalent compound. We do not mean to imply that the phosphonium oxide group (Ph_3PO) is not a good leaving group; indeed this is considered to be a strong possibility in the reaction of tertiary alcohols

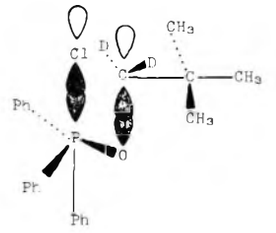


Figure 2. The decomposition of the intermediate $(CH_3)_3CCD_2$–$OPCl(C_6H_5)_3$ in a ${}_\sigma 2_s + {}_\sigma 2_a$ pericyclic reaction.

with tetrachloromethane–triphenylphosphine which leads to alkenes presumably due to prior formation of a tertiary carbenium ion.[3]

The ion-pair, four-centered mechanism is not unique in accounting for the stereochemistry, isotope effect, and the observed energetics. Indeed, Aneja, Davies, and Knaggs[7] proposed a $\sigma_{2_s} + \sigma_{2_a}$ thermal pericyclic reaction to account for the stereochemistry although there was no direct proof of this concerted process. However, this mechanism does account for the inversion of configuration and in a concerted process there could be almost equal C–Cl bond making and C–O bond breaking to account in full for the small isotope effect that we observed. First-order kinetics are also completely consistent with this mechanism. The intermediate that we have pictured in Figure 2 is that of a trigonal bipyramid (dsp^3) but there is no reason why we could not picture the intermediate as a square pyramid. What we do require is that one of the reacting groups be in the apical position (like the chloride in Figure 2) and the other group be in an equatorial position. Thus by breaking the P–Cl and the C–O bonds suprafacially (dark lobes) and also in a concerted process making a C–Cl bond via the front (dark) lobe of the Cl and the back (light) lobe of the C–O we have a symmetry-allowed ${}_\sigma 2_s + {}_\sigma 2_a$ pericyclic reaction in which the bonds are presumed to be heterolytically cleaved.

The one major flaw in the ${}_\sigma 2_s + {}_\sigma 2_a$ mechanism resides in the fact that the neopentyl system is only slightly hindered by front-side steric hindrance. Yet the neopentyl intermediate decomposes many times slower than benzyl, amyl, isoamyl, or 2-amyl alcohol intermediates. This is more in line with back-side steric hindrance than a concerted process involving front-side attack.

Examination of molecular models of the trigonal bipyramid structure (see Figure 2) would indicate that back-side displacement by chloride with this model would be a *very* difficult process. The ${}_\sigma 2_s + {}_\sigma 2_a$ mechanism is not really consistent with the slow decomposition of the neopentyl intermediate, although our other data do not rule out such a mechanism. At present, the intramolecular S_N2 displacement from the ion pair seems to be most consistent with both our data and that of other authors. Clearly, the energetics of decomposition of some simpler phosphonium intermediates are needed to more critically examine the microscopic decomposition pathways.

Experimental Section

^1H NMR spectra were determined with a JEOL C-60H spectrometer. Purity evaluations of all alcohols, cyclohexane, other internal standards, alkyl halides, carbon tetrachloride, and chloroform were performed on a Perkin-Elmer 990 gas chromatograph using a 1/8 in. × 12 ft column, packed with 20% FFAP on Chromosorb W. All melting points (uncorrected) were taken on a Thomas-Hoover capillary melting point apparatus.

Triphenylphosphine, obtained from Strem Chemical Co., was recrystallized from cyclohexane prior to use and found to have a melting point of 78 to 80 °C. Reagent grade carbon tetrachloride (greater than 99% purity) from Fisher Scientific Co. was distilled from triphenylphosphine, placed in a brown bottle under nitrogen, and stored in the dark prior to use. Deuterated chloroform of 99.8% purity was obtained from Thomas-Packard, Inc.

Typical ^1H NMR Procedure for Following Intermediate and Halide Formation. Neopentyl alcohol (mp 55–56.2 °C) was greater than 99% pure as determined by GLC. To a ^1H NMR tube were added 0.0969 g (1.1 mmol) of neopentyl alcohol, 0.300 g (1.14 mmol) of triphenylphosphine, 0.2 mL (0.319 g, 2.07 mmol) of carbon tetrachloride, 0.4 mL of chloroform-*d* and a trace amount of tetramethylsilane (Me_4Si) as an internal ^1H NMR standard. In some cases, a known amount of cyclohexane (99% pure) was added as an internal standard for integration purposes. The reaction was scanned for a period of 24 h. The disappearance of alcohol was followed by noting the area change in the OCH_2 peak and the *tert*-butyl peak of the neopentyl alcohol.

Heteronuclear Decoupling Experiment. A solution of 0.100 g of neopentyl alcohol, 0.300 g of triphenylphosphine, 0.2 mL of carbon tetrachloride, 0.4 mL of chloroform-*d*, and tetramethylsilane (trace) was added to a ^1H NMR tube and allowed to react at room temperature for 4 h. The reaction was scanned by ^1H NMR and the appearance of a doublet indicative of ^{31}P coupling was noted. Irradiation of the sample at the ^{31}P resonance frequency collapsed the doublet to a singlet.

Competitive Kinetics as Determined by ^1H NMR. To a high-precision ^1H NMR tube, 0.044 g (0.500 mmol) of neopentyl alcohol, 0.051 mL (0.053 g; 0.490 mmol) of benzyl alcohol, 0.300 g (1.143 mmol) of triphenylphosphine, 0.054 mL (0.77 g; 0.914 mmol) of cyclohexane, deuterated chloroform, and tetramethylsilane were added. After an initial scan, with no carbon tetrachloride, 0.200 mL (0.292 g; 1.898 mmol) of carbon tetrachloride was added and the reaction was observed for a period of 24 h. The areas of the CH_2 peaks were observed both for the disappearance of the alcohol and the formation of halide and/or intermediate. Three duplicate runs were examined.

Typical Gas-Liquid Phase Chromatographic Procedure for Following the Disappearance of Alcohol and Formation of Halide. All GLC data were determined with a Perkin-Elmer 990 gas chromatograph. Two columns were used for both the molar response data and the competitive kinetics: a 1/8 in. × 12 ft column packed with 20% FFAP on Chromosorb W and a 1/8 in. × 20 ft silicone column. The reaction was first examined using an excess of chlorinating agent and a minimum of alcohol then the reaction was followed using an excess of alcohol and a minimum of chlorinating agent. The triphenylphosphine used was recrystallized from cyclohexane. Just prior to use, the chloroform was shaken with alumina to remove traces of ethanol stabilizer. All of the reactants used, except isoamyl alcohol (3-methyl-1-butanol), were found to be greater than 99% pure as determined by GLC. Isoamyl alcohol was purified by preparatory GLC, using a 0.5 in. × 20 ft FFAP column in a preparative Varian 1800 Aerograph gas chromatograph. The internal standards, *o*-chlorotoluene, ethylbenzene, and *p*-dichlorobenzene, were also found to be greater than 99% pure. The carbon tetrachloride was distilled from triphenylphosphine. A vacuum apparatus was used for trapping the volatile reactants (and thus quenching the reaction). The apparatus was made by Lab Glass, Inc. and consisted of three U-tube traps connected to each other in series with a ball and socket connection and protected at each end with glass stopcock valves. This evacuation apparatus was connected at one end to a rotary evaporator and at the other end to a vacuum pump. Three Dewars of liquid nitrogen were used to cool the traps. Prior to following the competitive kinetics of the alcohols, the following molar responses were obtained: (i) 1-pentanol, 2-pentanol, 3-methyl-1-butanol vs. o-chlorotoluene in chloroform–carbon tetrachloride, (ii) 1-chloropentane, 2-chloropentane, 3-methyl-1-chlorobutane, and *o*-chlorotoluene in chloroform–carbon tetrachloride vs. *p*-dichlorobenzene and/or vs. ethylbenzene.

In examining the relative competitive kinetics of this reaction two pairs of alcohols were used: (1) 1-pentanol vs. 2-pentanol; and (2) 1-pentanol vs. 3-methyl-1-butanol. Each of the two pairs of alcohols were reacted under conditions of excess chlorinating agent and under conditions of excess alcohol. Each reaction was run in duplicate.

The following description of a reaction using the first pair of alcohols illustrates a typical kinetic run. Just prior to use, all glassware was cleaned first with a detergent–water solution, rinsed with distilled water then acetone, dried in a 110 °C oven for an hour, and cooled by a stream of dry nitrogen. Into a 10.00-mL volumetric flask was placed 0.24 mL (0.194 g; 2.2 mmole) of 1-pentanol, 0.23 mL (0.194 g; 2.2 mmol) of 2-pentanol, 0.18 mL (0.193 g; 1.5 mmol) of *o*-chlorotoluene, and 2.31 g (8.8 mmol) of triphenylphosphine. The reaction was timed after dilution to 10.00 mL with a 60:40 (v/v) chloroform–carbon tetrachloride mixture. A 1-mL aliquot was withdrawn from the reaction solution immediately after the addition of the chloroform–carbon tetrachloride mixture. The volumetric flask with the remaining reaction mixture was placed in a 25 °C water bath where it remained

for the duration of the examination. The 1.00-mL aliquot was transferred to a 50-mL round-bottomed flask which in turn was connected to a rotary evaporator. A 30–32 °C water bath was raised into place underneath the round-bottomed flask and the spin rate of the rotary evaporator was turned to its highest speed. The vacuum apparatus had previously been evacuated and the Dewars of liquid nitrogen were raised into place to cool the traps. The valve connecting the evaporator to the vacuum apparatus was opened slowly, care being taken to trap as much of the vapors as possible in the first trap. After this was accomplished, the needle valve on the manifold was closed slowly and the system, which was now under a vacuum of 0.1 mm, was evacuated for 0.5 h. At that time, the valves to the vacuum pump and the rotary evaporator were closed. Then the set of valves to each U-tube were closed and the Dewars were lowered to allow the U-tubes' contents to thaw. To two 1.00-mL calibrated volumetric flasks approximately 1 mmol of *p*-dichlorobenzene was added. Using chloroform as a wash, the liquid from the three U-tube traps was placed in one of the flasks while the syruplike material which remained in the 50-mL round-bottomed flask was dissolved in chloroform and placed in the remaining volumetric flask. These flasks were filled to the mark with chloroform. Then the material from each flask was transferred to a labeled 5-mL Erlenmeyer flask, corked, covered with Nalge plastic, and placed in the refrigerator until ready for GLC analysis. At that time they were placed on ice until the GLC analysis was completed.

The areas of the peaks obtained by GLC were determined first by the standard peak height times peak width at half-height and in the last stages of this research by direct area reading via a voltage to frequency converter (Model 2210 by Dymec) and an electronic counter (Model 2725 by Simpson).

Competitive Kinetics. ^{1}H NMR competitive kinetics between neopentyl alcohol and benzyl alcohol were run at 25 °C using cyclohexane as an internal standard. The area of the cyclohexane standard was divided by 12 to obtain a standard area for hydrogen. The $\mathbf{CH_2OH}$ and $\mathbf{CH_2Cl}$ areas of the benzyl alcohols, benzyl chloride, neopentyl alcohol, and neopentyl intermediate were normalized to the standard, and the relative reactivity of the alcohols was determined from the disappearance of the alcohol (assuming the alcohol molecularity was first order) using the expression

$$k_A/k_B = \log [[A_i]/[A_f]] / \log [[B_i]/[B_f]]$$

where k_A/k_B is the relative rate constant for reaction with alcohol A and alcohol B while $[A_i]/[A_f]$ and $[B_i]/[B_f]$ are the ratios of the initial to final alcohol concentrations for alcohols A and B, respectively.[16] For GLC kinetics, the amounts of alcohol and alkyl halides were determined from molar response data with given standards. The same kinetic expression was used to determine relative rates of disappearance of alcohols.[16]

Preparation of 1,1-Dideuterio-2,2-dimethylpropanol (10). To a three-necked 500-mL flask equipped with dropping funnel, condenser, and thermometer was added 5.403 g (0.128 mole) of lithium aluminum deuteride (99% Stohler Isotope) in 250 mL of anhydrous ether. To this solution was added 14.0 g (0.12 mol) of methyl trimethylacetate (methyl pivalate 99% by GLC; Aldrich Chemical) in 125 mL of ether in a dropwise manner for 45 min at 0 °C and 30 min at room temperature. When the supernatant liquid showed no carboxyl stretch (1710 cm^{-1}) in the infrared, the reaction was quenched with wet sodium sulfate followed by 6 M sulfuric acid. The ether layers were combined, washed with saturated sodium chloride, and dried over anhydrous potassium carbonate. The ether was carefully distilled in a Todd column and the product was distilled from a microdistillation flask. A forerun (3 g) containing some ethyl ether was not used but the main fraction (6.0 g; 0.68 mol, 57%) had bp 106 °C (725 Torr) and mp 49–50 °C. Theory would predict 16.66 atom % excess D; 16.25 atom % excess D was found (Josef Nemeth Labs, Urbana, Il.). This corresponds to 1.95 D/molecule.

Preparation of Kinetic Samples. A 3.300-g sample of triphenylphosphine (12.6 mmol) and 0.660 g of neopentyl alcohol (7.5 mmol) were placed in a 50-mL flask. To this flask was added 2.20 mL of tetrachloromethane (22.8 mmol) and 5.00 mL of chloroform-*d* as solvent. This solution was allowed to stand about 5 h and was monitored for intermediate formation by ^{1}H NMR spectroscopy. After the intermediate had formed, the solution was transferred into ^{1}H NMR tubes and sealed. This same procedure was followed for the 1,1-dideuterio-2,2-dimethylpropanol except that 0.665 g (7.5 mmol) of the latter alcohol was used. The sealed NMR tubes were placed in a thermostated bath and removed from time to time and quenched by immersing the tubes in an isopropyl alcohol ice bath at −12 °C. The quenched samples were placed in a freezer and the ^{1}H NMR's were all run at the same time.

Kinetics. The fraction reacted (Φ) was determined as the height of the *tert*-butyl portion of the neopentyl chloride isomer (δ 0.967) divided by the height of the *tert*-butyl portion of the intermediate (δ 1.033) plus the height of the *tert*-butyl portion of the neopentyl chloride. Using the standard first-order equation $kt = \ln (1/(1 - \Phi))$ we obtained good plots of $\ln (1/(1 - \Phi))$ vs. t. All rates were obtained using least squares and correlation coefficients of 0.997 to 0.999 were obtained for all rates.

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Registry No.—**6,** 66085-08-3; **10,** 7210-87-9; neopentyl alcohol, 75-84-3; triphenylphosphine, 603-35-0; carbon tetrachloride, 56-23-5; methyl trimethylacetate, 598-98-1; 1-pentanol, 71-41-0; isoamyl alcohol, 123-51-3; 1-chloropentane, 543-59-9; isoamyl chloride, 107-84-6; 2-pentanol, 6032-29-7; 2-chloropentane, 625-29-6; $(CH_3)_3CCD_2OPCl(C_6H_5)_3$, 66085-09-4.

Supplementary Material Available: Listing of a least-squares plot for E_{act} and two tables on relative rates with excess and minimum of chlorinating agent (3 pages). Ordering information is given on any current masthead page.

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Carbon-13 Kinetic Isotope Effects on Pyruvate Decarboxylation. 2. Solvent Effects in Model Systems[1]

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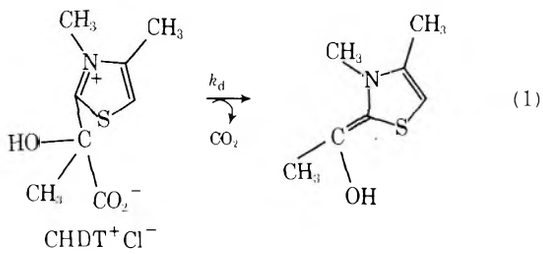
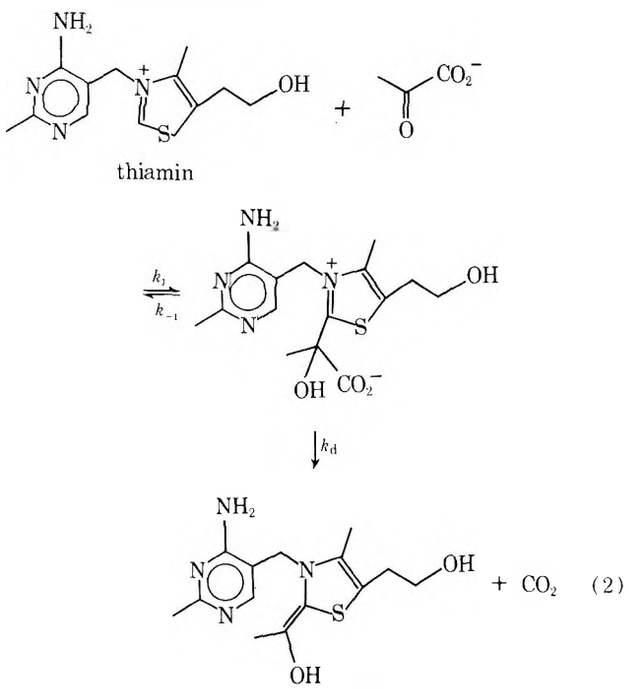
Carbon-13 kinetic isotope effects were determined for the decarboxylation of pyruvate by thiamin and for the decarboxylation of 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride (a covalent pyruvate–thiamin adduct) in water and in aqueous ethanol. The kinetic isotope effect for the decarboxylation step in the second system increased from 1.051 in H_2O to ~1.058 in 50% v/v ethanol. The isotope effect in the thiamin catalyzed model reaction increased from the 0.992 inverse effect observed in H_2O to 1.007 in 50% aqueous ethanol. The rate of decomposition of the covalent thiamin–pyruvate adduct to reactants relative to its rate of decarboxylation is greater in ethanol than in water. Further, the results suggest that the changes of the vibrational force constants in going from the ground state to the transition state are greater in aqueous ethanol than in water.

Carbon-13 kinetic isotope effect (KIE) studies provide a convenient, if seldom employed, technique for elucidating the rate-determining step in a multistep reaction mechanism which involves C–C bond breaking or making. We recently reported ^{13}C KIE values[2] for the decarboxylation of pyruvate by yeast pyruvate decarboxylase (E.C.4.1.1.1) and for two model systems: (1) 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride ($CHDT^+Cl^-$), a model KIE for the decarboxylation step,



$CHDT^+Cl^-$ (1)

and (2) thiamin catalyzed decarboxylation, a model KIE for the two steps, covalent pyruvate–coenzyme adduct formation followed by decarboxylation.



(2)

The experimental KIE values of 1.051 for reaction 1, and 0.992 for reaction 2, and the KIE of 1.002 to 1.011 observed for the holoenzyme-catalyzed reaction were interpreted to mean that *in both the thiamin model and in the enzymic reaction decarboxylation is not rate limiting*, i.e., $k_{-1}/k_d < 1$.

Attachment of a fluorescent dye to the active site of pyruvate decarboxylase has suggested the existence of a hydrophobic environment.[3] In addition, model studies closely resembling those in eq 1 and 2 demonstrated that the reactions proceed faster in ethanol than in water[4] and have led Lienhard's group to suggest that the enzyme may accelerate the reaction by creating a low polarity environment around the active site. Based on these suggestions, we undertook a study to demonstrate the effect of the solvent dielectric constant on the rate-limiting step in the model reaction depicted in eq 2.

Results and Discussion

The isotope effects were calculated according to Bigeleisen's formula[5] from data obtained by measuring isotope ratio $^{45}CO_2/^{44}CO_2$:

$$k^{12}/k^{13} = \frac{\log(1-f)}{\log\left(1 - f\frac{N_x}{N_{x0}}\right)} \quad (3)$$

where N_x is the isotope ratio at low fractional conversion f corrected for the natural abundance of $^{12}C^{16}O^{17}O$, and N_{x0} is the corrected ratio at 100% reaction ($f = 1.0$).

***CHDT*$^+$*Cl*$^-$**. Table I summarizes the data in water and in aqueous ethanol. Clearly, the KIE increases with increasing ethanol content. The rate of decarboxylation has also been found to increase with added ethanol.[4a] Even with the large f value employed (this was necessitated by the limited quantity of substrate available for this study) error analysis[5b] indicates less than ±0.002 uncertainty in the isotope effect due to the cumulative uncertainties of f and N_x measurements.

Solvent effects on heavy-atom KIE measurements are rare in the literature. The solvent isotope effect on malonic acid decarboxylation was reported to be small: 1.034 in H_2O at 137 °C;[6] 1.032 in dioxane at 99.1 °C;[7] and 1.032 in quinoline at 138 °C.[8] Cromartie and Swain[9] reported $k_{water}/k_{ethanol}$ chlorine isotope effects of 0.999 84 for cyclization of 2-chloroethanol and 1.000 56 for the reverse reaction. In *tert*-butyl alcohol the solvent isotope effect was 1.000 36 for the forward and 1.000 30 for the reverse reaction.

Since $CHDT^+Cl^-$ retains its dipolar ionic character in the range of ethanol–water mixtures employed here,[4a] one can write the solvent effect in terms of a single rate constant for the two isotopically labeled species:

$$\frac{(k_d/k_d^*)_{30\%\ \text{ethanol}}}{(k_d/k_d^*)_{H_2O}} = \frac{1.054}{1.051} \simeq 1.003 \quad (4)$$

and

Table I. ^{13}C Kinetic Isotope Effect on $CHDT^+Cl^-$ Decarboxylation

Temp, °C	Conc $CHDT^+Cl^-$, mM, in solvent	f[a]	$N_x \times 10^6$ [b]	N_{x0}[c]/N_x		k^{12}/k^{13} [d]
45.6	16.8 in H_2O	0.1914	10124	1.0459		1.0511
45.6	16.8 in H_2O	0.1988	10131	1.0452		1.0506
					Av	1.0509[f]
45.6	15.8 in 30% ethanol[e]	0.1897	10104	1.0480		1.0534
45.6	15.8 in 30% ethanol	0.2275	10113	1.0471		1.0537
					Av	1.0536[f]
25.6	15.8 in 50% ethanol[e]	0.2004	10061	1.0525		1.0583
25.6	15.8 in 50% ethanol	0.2223	10080	1.0505		1.0574
					Av	1.0581[f]

[a] Fractional reaction determined from kinetic data in ref 4a. [b] Isotope ratio at fractional reaction f. [c] Isotope ratio at $f = 1.00$; equal to 10588 ± 9 for five separate determinations with 95% confidence limits. [d] Calculated isotope effect according to eq 3. [e] 30% ethanol–70% H_2O (v/v). [f] In ref 2 we demonstrated that the enzymatic KIE at pH 5.00 is temperature independent between 10 and 37 °C.

$$\frac{(k_d/k_d^*)_{50\%\ \text{ethanol}}}{(k_d/k_d^*)_{H_2O}} = \frac{1.058}{1.051} \simeq 1.007 \qquad (5)$$

If C–C stretching is the principal contribution to the KIE, these results would imply that the changes in the C–C stretching force constant in going from the reactant to the transition state are greater in aqueous ethanol than in water.[10]

Thiamin-Catalyzed Decarboxylation. Table II summarizes the data in 50% (v/v) ethanol. The most striking feature of the results is that the KIE changes from an inverse (0.992) to a normal (1.007) value on transferring the decarboxylation from water to aqueous ethanol. We have shown[2] that the rate expression for contrasting the ^{12}C and $^{13}C^*$ isotopic reaction rates is:

$$k^{12}/k^{13} = k_1/k_1^* \frac{(1 + [k_{-1}^*/k_d^*])}{(1 + [k_{-1}/k_d])} \qquad (6)$$

It has been found previously that the ratio k_{-1}/k_d is small, i.e., the rate of decomposition of the thiamin–pyruvate adduct into reactants is slower than the rate of decarboxylation.[2] The observed ratio of k^{12}/k^{13} is largely determined by the secondary isotope effect on k_1 and k_{-1}. However, the observed change in k^{12}/k^{13} cannot be explained solely on the basis of a solvent isotope effect on k_1 and k_{-1}. For the decarboxylation step of the $CHDT^+Cl^-$ system the change is 1.007. A transfer between solvents would probably induce smaller changes in the secondary isotope effects k_1/k_1^* and k_{-1}/k_{-1}^* respectively than in k_d/k_d^*. In order to account for the observed change of k^{12}/k^{13} by a factor of 1.015 (0.992 to 1.007), according to eq 6, an increase of the ratio of k_{-1}/k_d is required, i.e., $(k_{-1}/k_d)_{50\%\ \text{ethanol}} > (k_{-1}/k_d)_{H_2O}$. We therefore conclude that the rate of decomposition of the thiamin–pyruvate adduct into reactants relative to the rate of its decarboxylation is enhanced in aqueous ethanol as compared with water. Our conclusions are in satisfactory qualitative agreement with earlier kinetic measurements. It was found that $k_{d,\text{ethanol}}/k_{d,H_2O}$ is ca. 9000 for $CHDT^+Cl^-$ [4a] and that k_{-1} for the lyate ion catalyzed decomposition of the thiazolium–ethyl pyruvate covalent adduct to reactants is ca. 4×10^4 faster in ethanol than in water.[4b]

Table II. ^{13}C Kinetic Isotope Effects on Pyruvate Decarboxylation Catalyzed by Thiamin in 50% Ethanol (v/v) Buffered by 0.05 M $NH_4^+Cl^-$ with $(NH_4^+)/(NH_3) = 2$

Pyruvate, M	Thiamin, M	f[a]	N_x[b]	N_{x0}[c]/N_x	k^{12}/k^{13} [d]
0.1818	0.0455	0.0119	10534	1.0048	1.0048
0.0909	0.0455	0.0075	10510	1.0071	1.0071
0.0909	0.0455	0.0075	10505	1.0076	1.0076
0.0909	0.0455	0.0075	10528	1.0054	1.0054
0.0909	0.0455	0.0075	10495	1.0086	1.0086
0.0909	0.0455	0.0075	10490	1.0090	1.0090
0.0909	0.0455	0.0075	10504	1.0077	1.0077
0.0909	0.0455	0.0075	10499	1.0082	1.0082
				Av	1.0073 ± 0.0012
In H_2O[e]					0.9921 ± 0.0014

[a] Fractional reaction. [b] Isotope ratio at the fractional reaction f. [c] Isotope ratio at $f = 1.0$; the average value of the $CHDT^+Cl^-$ N_{x0} (see Table I, footnote c) and the holoenzyme N_{x0} (Table IV, ref 2, the average of 16 determinations) as these two values are within experimental error identical. [d] Calculated isotope effect according to eq 3. [e] From ref 2, Table II; the average of 12 determinations in the pH range of 6.5–8.6.

Finally, if the active site of holopyruvate decarboxylase indeed resembles alcohol in its microenvironment rather than water, these results suggest that part of the observed enzymic KIE (1.002 to 1.011 depending on pH) is due to the apolar environment. In the absence of environmental factors the observed KIE would be even smaller or inverse.

Experimental Section

Reagents. Sodium pyruvate and thiamin hydrochloride were purchased from Sigma and were used without further purification. Inorganic reagents were of highest purity available from Fisher Scientific. Buffers were prepared from sodium acetate and acetic acid (pHs 5.00 and 5.50), sodium citrate and citric acid (pH 6.00), monobasic and dibasic phosphate (pHs 6.50, 7.00, and 7.50), and sodium borate (pHs 8.00 and 8.60). $CHDT^+Cl^-$ was kindly provided by Dr. G. E. Lienhard of Dartmouth Medical School.

pH-stat titration was employed in the determination of the low conversion reaction times of the thiamin-catalyzed decarboxylation. The decarboxylated product (eq 2) is quickly protonated under the conditions employed (pH <8.6, $pK_a = 17$[4a]) and OH^- production can be used to monitor the reaction rate.[11] A Radiometer (Copenhagen) pH meter Model 26 equipped with titrator 11, autoburet ABU 12, stirring system, and recorder REA (300) was used. The chart speed was set at 1 min/cm or 30 s/cm. The titration speed was set at 5, 10, or 20 depending on the rate of acid consumption.

In a typical determination at low fractional conversion 2.00 mL of 0.2 M pyruvate (adjusted to pH 5.00 and flushed for 30 min with CO_2-free high-purity N_2) was pipetted into a plastic beaker on a titrigraph that was equipped with a plastic stirrer. With the recorder running, thiamin solution (CO_2 free) was introduced via a microliter pipet. Three samples were run and recorded. On the same day a scaled up reaction was run to collect CO_2 employing 100 mL of 0.2 M pyruvate and scaled up thiamin. The fraction, f, in the scaled up reaction could be calculated from the number of moles of 0.01 N HCl consumed divided by the total number of moles of pyruvate. The Warburg respirometer was also employed in the determination of the fractional reaction of thiamin-catalyzed decarboxylation. The kinetic information from ref 4a was employed to estimate the fractional reaction of $CHDT^+Cl^-$.

Reaction under CO_2-free N_2 and Collection of CO_2. The entire procedure was performed on a high-vacuum line. First the reaction vessel (a three-neck flask equipped with separator funnel, drying tube, and a syringe cap) was purged three times (filled then evacuated to below 50 μm) with high-purity CO_2-free N_2. The reaction vessel was

filled with CO_2-free N_2 and 100 mL of pyruvate solution (previously degassed by bubbling through it CO_2-free N_2 for at least 30 min) was injected through the sidearm. The solution was stirred and thermostatted at 30 °C for 30 minutes. Next 0.5 mL of thiamin (or $CHDT^+Cl^-$ sans pyruvate) was injected through a ruhher septum to initiate the reaction. The reaction was quenched (syringe cap) with 5 mL of concentrated H_2SO_4 after ca. 200 μmol of CO_2 had evolved (as calculated from the f values determined above).

The reaction vessel was then attached to the vacuum line at a different point and frozen with liquid N_2 and the nitrogen in the vessel was removed by the vacuum pump until no further significant pressure decrease in vacuum gauge reading could be observed. The flask was then warmed slightly and refrozen in a dry ice–acetone bath and the CO_2 was distilled into a U tube which was cooled in liquid N_2. The liquid nitrogen was replaced by dry ice and the CO_2 was passed to the Toepler pump bulb. The dry ice–acetone was removed from the U tube and the condensed gases were pumped until the vacuum gauge read below 50 μm. Then the gas was transferred to a sample tube for mass spectrometric measurement. In the reaction catalyzed by thiamin, CO_2 was purified by passage through H_2SO_4.

Mass Spectrometric Analysis. The isotope ratio ($^{13}CO_2/^{12}CO_2$) was determined on a Consolidated-Nier Model 21-201 isotope ratio mass spectrometer.[13] The atom fraction of C^{13}, N_x, corrected for $C^{12}O^{16}O^{17}$, was calculated from the expression

$$10^6 N_x = \frac{\bar{r}_{\text{sample}} 11134}{\frac{1}{2}(\bar{r}_{\text{tank before}} + \bar{r}_{\text{tank after}})} - 800$$

where $\bar{r}_{\text{sample}}$ is the average ratio of six readings of CO_2 sample and $\bar{r}_{\text{tank before}}$ and $\bar{r}_{\text{tank after}}$ are the average ratios of six readings of tank CO_2 (Matheson Research Purity) measured before and after the sample measurement, respectively. The number 800 was provided by the manufacturer to compensate for the O^{17} isotope ratio $(C^{12}O^{16}O^{17})\cdot(11134 \pm 5) \times 10^{-6}$ is the average value of the 1362 readings of the 45/44 mass ratio of tank CO_2 during the entire course of the present experiments.

N_{x0} for the thiamin-catalyzed reaction was the average value of the N_{x0}[2] determined for $CHDT^+Cl^-$ and of the N_{x0} determined for the holoenzyme-catalyzed reaction[2] as these two are in close accord. This had to be done since the thiamin-catalyzed reaction leads to acetolactate (and thence acetoin) so that the CO_2 is liberated from two sources. However, at low conversion (even with a 100% error in the estimate of f in the range of $f \simeq 0.01$) the source of CO_2 is exclusively pyruvate (rather than acetolactate) since the subsequent steps are much slower.

Registry No.—$CHDT^+Cl^-$, 29510-46-1; sodium pyruvate, 113-24-6; thiamin hydrochloride, 67-03-8.

References and Notes

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Oxidation of Olefins with Peroxouranium Oxide ($UO_4 \cdot 4H_2O$)[1]

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Peroxouranium oxide was found to be an effective oxidizing agent for alkenes. The oxidations are suggested to proceed through an oxyuranylation path with resulting carbocationic rearrangement of the intermediates. The used reagent may be recovered and regenerated effectively.

Although many dioxygen–metal compounds are known,[2] little is known about their reactions. The preparation of peroxouranium oxide from uranyl nitrate and hydrogen peroxide has been known for nearly a century.[3] The structure has been established by Gordon and others[4] as being a true peroxo complex, $UO_2(O_2)\cdot 4H_2O$.[2a] The aqueous chemistry of peroxouranium(VI) has been found to be complicated. Peroxouranium oxide tetrahydrate forms peruranates of varying composition with aqueous hydrogen peroxide, culminating in the formation of the most stable UO_8^{2-} species.[2b] So far the oxidizing ability of UO_4 in organic systems was not explored.

Results and Discussion

Peroxouranium oxide tetrahydrate was found to be an effective oxidizing reagent for hydrocarbons, particularly olefins. Data are summarized in Table I. Ring-contracted, ring-expanded, and epoxidized products were obtained. The reaction is viewed as proceeding via the complexation of the olefin by the coordinatively unsaturated uranium. The increasing electron density at the metal results in a lengthening of the metal–dioxygen bond until a metal–carbon bond is formed, while the developing charge-deficient carbon forms a bond to the displaced oxygen. The cyclic intermediate de-

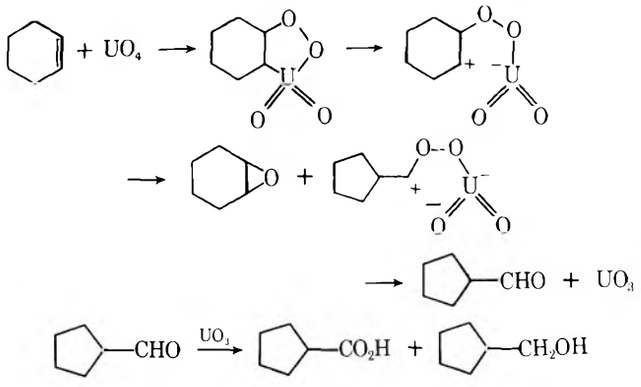
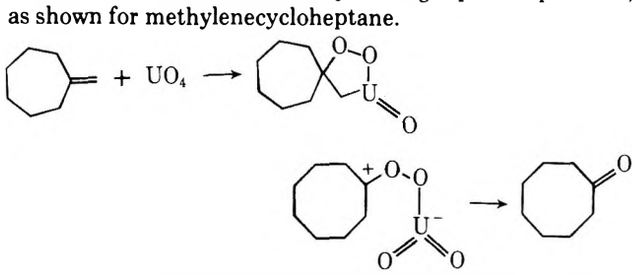


Table I. Oxidation of Olefins with Peroxouranium Oxide

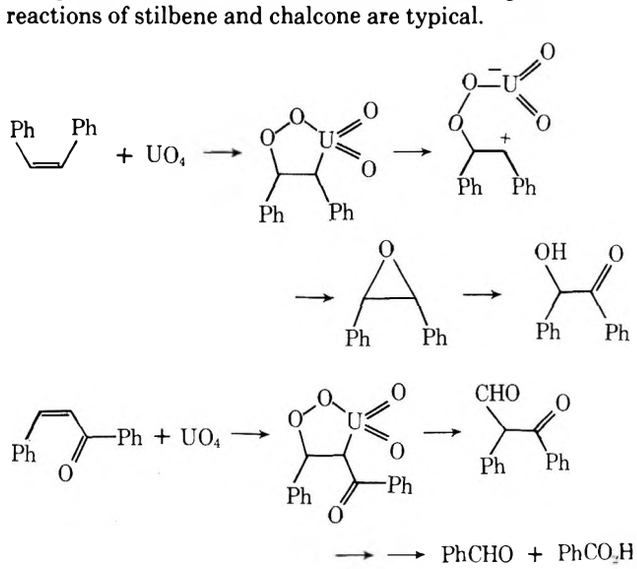
Olefin	Registry no.	% yield of oxygenated products[a]	Product distribution[b]	Registry no.
Cyclohexene	110-83-8	34	Cyclopentanecarboxylic acid (46%)	3400-45-1
			Cyclopentanecarbinol (54%(	3637-61-4
1-Methylcyclohexene	591-49-1	58	Methyl cyclopentyl ketone	6004-60-0
Cyclooctene	931-88-4	44	Cyclooctene oxide (83%)	286-62-4
			Cyclohexanecarboxylic acid (17%)	1460-16-8
Cyclododecene	1501-82-2	43	Cyclododecene oxide (69%)	286-99-7
			Cycloundecanecarboxylic acid (31%)	831-67-4
Methylenecycloheptane	2505-03-5	30	Cyclooctanone	502-49-8
Methyleneadamantane	875-72-9	48	Adamantanone	700-58-3
2-Methylenenorbornane	497-35-8	31	2-Bicyclo[3.2.1]octanone	5019-82-9
			3-Bicyclo[3.2.1]octanone	14252-05-2
1,1-Diphenylethylene	530-48-3	53	Benzophenone (83%)	119-61-9
			α-Methylbenzhydrol (17%)	599-67-7
4-Phenyl-1-butene	768-56-9	64	3-Phenylpropionic acid (50%)	501-52-0
			4-Phenyl-2-butanone (50%)	2550-26-7
Chalcone	94-41-7	50	Benzaldehyde (11%)	100-52-7
			Benzoic acid (89%)	65-85-0
trans-Stilbene	103-30-0	36	Stilbene oxide (12%)	17619-97-5
			Benzoin (88%)	119-53-9

[a] Yields reported are isolated yields of all oxygenated products recovered. [b] Products were identified by isolation, degradation, and derivatization as well as comparison of spectral properties with those of authentic samples.

composes with rearrangement and/or epoxidation. A somewhat similar mechanism was recently also involved by Sharpless et al.[5] in the chromyl chloride oxidation of olefins. Aldehydes formed under the reaction conditions quickly undergo Cannizzaro-type oxidation–reduction reactions which seem to be promoted by UO_3, as shown for the reaction of cyclohexene. It can be suggested that exocyclic olefins might react via a similar mechanism to yield ring expanded products, as shown for methylenecycloheptane.



The reaction of exocyclic olefins, however, was accompanied by complete oxidative cleavage of the methylene group to yield the corresponding carbonyl compound in several examples studied. Alicyclic olefins reacted to yield numerous oxygenated products derived from oxidation and rearrangement. The reactions of stilbene and chalcone are typical.



The use of excess hydrogen peroxide in the reaction is not essential as the same products were formed in control experiments when pure peroxouranium oxide ($UO_4 \cdot 4H_2O$) was used alone in dioxane suspension. Peroxouranium oxide thus clearly is an effective oxidizing agent. The use of hydrogen peroxide with $UO_4 \cdot 4H_2O$ is known to form a variety of peroxo species as discussed earlier.[2b] These additional peroxo species seem to enhance the reactivity of the reaction system, i.e., yields are higher for similar reaction times. However, the product distribution is not sensitive to variation of the amount of excess hydrogen peroxide used. Furthermore, pure sodium peruranate, Na_2UO_8, prepared by the method of Alcock,[4] is unreactive under the reaction conditions. Presumably the metal is coordinatively saturated and is no longer free to interact with the olefin. The effect of excess hydrogen peroxide must therefore lie in the formation of reactive intermediate peroxo species.

The oxymetalation mechanism[6a,b] formulated for the oxidation reaction of olefins by $UO_4 \cdot 4H_2O$ is well known for oxidation reactions with mercury,[6c] thallium,[7] and lead.[8] A similar oxymetalation reaction has been proposed for the reaction of MoO_5 with olefins.[9] Mimoun and co-workers base their conclusions on the proposal that peracids react to form an epoxide via a 1,3-dipolar interaction.[10] Raciczewski has found evidence for metal–carbon interaction in the reactions of pertungstannic acid.[11] Similar interactions were observed with vanadium(V).[12]

The Rh(I) dioxygen complex catalyzed oxidation of hexene[13] and the iridium promoted styrene to acetophenone[14] transformations both yielded products which would be expected by an oxymetalation reaction path. The products found in the reaction of $UO_4 \cdot 4H_2O$ are not simply derived by the Lewis acid promoted rearrangement of the formed epoxide.[15] When cyclooctene oxide was heated with either UO_3 or $UO_4 \cdot 4H_2O$ under the usual reaction conditions, the unchanged starting material was recovered. The free-radical mechanism proposed by Collman[16] and Kurkov[17] in the reaction of cyclohexene and cyclopentene with rhodium and iridium compounds would result in the formation of hydroperoxide intermediates. Products derived from such intermediates were not isolated from the reactions of $UO_4 \cdot 4H_2O$. Peroxouranium oxide can be regenerated from the UO_3 product by digestion with nitric acid and reprecipitation with hydrogen peroxide.

The reagent can therefore be recycled without loss of the metal. $UO_4 \cdot 4H_2O$ reactions thus are indeed dependent only on the hydrogen peroxide used, affording an economical route to many oxidations.

Experimental Section

Peroxouranium Oxide Tetrahydrate. Peroxouranium oxide tetrahydrate was prepared by the method of Alcock.[4] To 50.5 g (0.1 mol) of uranyl nitrate hexahydrate (Mallinckrodt) dissolved in 500 mL of 10% nitric acid was added 35 mL of 30% hydrogen peroxide. The pale yellow peroxouranium oxide hydrate precipitated from solution, was separated by suction filtration washed with absolute ethanol, and was dried overnight at 50 °C. The material recovered by filtration from oxidation reactions with peroxouranium oxide was carefully dissolved with stirring in concentrated nitric acid. After stirring for 30 min, the nitric acid solution was diluted to 10% and excess 30% hydrogen peroxide was added. The resultant precipitate was filtered, washed, and dried as described above.

Oxidation of Cyclooctene with $UO_4 \cdot 4H_2O$. Method A. To 3.74 g (0.01 mol) of $UO_4 \cdot 4H_2O$ suspended in 100 mL of tetrahydrofuran in a 250-mL round-bottom flask equipped with a reflux condensor was added 1.10 g (0.01 mol) of cyclooctene. The reaction mixture was heated under reflux for 18 h, cooled, filtered, quenched, and extracted as described. Evaporation of the solvent yielded an alcohol, IR (neat) 3440 (s, OH) cm^{-1}, whose identity was confirmed by Jones oxidation. Cycloheptanecarboxylic acid (1.2 g; 84% yield), IR (neat) 3300 (w, OH) and 1710 cm^{-1} (s, C=O), was obtained.

Method B. To 3.38 g (0.009 mol) of $UO_4 \cdot 4H_2O$ suspended in 100 mL of dioxane and 20 mL of 30% hydrogen peroxide in the previously described apparatus was added 0.96 g (0.009 mol) of cyclooctene. The reaction mixture was heated under relux for 20 h, cooled, filtered, quenched, and extracted as described. Evaporation of the dried solvent yielded 0.51 g (44% yield overall) of product. The product was chromatographed on aluminum oxide (Merck) eluting with 250 mL of petroleum ether (bp 37–56 °C), 250 mL of benzene, and 250 mL of chloroform. From the petroleum ether and benzene solutions was isolated 0.42 g (83% of product) of cyclooctene oxide identified by isomerization with boron trifluoride etherate to cyclooctanone, IR (neat) 1700 cm^{-1} (s, C=O). Evaporation of the chloroform solution yielded 0.09 g (17% yield) of cycloheptanecarbinol, IR (neat) 3440 cm^{-1} (s, OH), identified by Jones oxidation to cycloheptanecarboxylic acid, IR (neat) 3300 (w, OH) and 1710 cm^{-1} (s, C=O).

Oxidation of 1,1-Diphenylethylene with $UO_4 \cdot 4H_2O$. 1,1-Diphenylethylene (1.8 g, 0.01 mol) was oxidized according to method B. Crude product (0.960 g; 53% overall yield) was isolated. The material was chromatographed on 30 g of adsorbent alumina eluting with 330 mL of benzene followed by 250 mL of chloroform. Evaporation of the benzene solution yielded 0.72 g (83% yield of product) of benzophenone, IR (CCl_4) 1660 cm^{-1} (s, C=O). Evaporation of the chloroform solution yielded 0.14 g (17% of product) of 1,1-diphenyl-1-ethanol, IR (neat) 3460 cm^{-1} (s, OH).

Oxidation of 4-Phenyl-1-butene with $UO_4 \cdot 4H_2O$. 4-Phenyl-1-butene (1.32 g, 0.01 mol) was oxidized by method B. A product yield of (0.95 g; 64% overall) was isolated. Extraction of an ethereal solution of the product with aqueous base yielded after acidification and extraction 0.47 g (50% of product) of 3-phenylpropionic acid, IR (neat) 3400 (s, OH) and 1715 cm^{-1} (s, C=O). Mass spectrum of the product showed an M − 1 peak at *m/e* 150. Evaporation of the ethereal solution remaining after basic extraction after drying yielded 0.48 g (50% of product) of 4-phenyl-2-butanone, IR (neat) 1720 cm^{-1} (s, C=O). Mass spectrum of the product showed a molecular ion peak at *m/e* 148.

Oxidation of Methylenecycloheptane with $UO_4 \cdot 4H_2O$. Methylenecycloheptane (0.70 g, 0.006 mol) was oxidized with 2.14 g (0.006 mol) of $UO_4 \cdot 4H_2O$ by method B. Cyclooctanone (0.23 g; 30% yield) was isolated, IR (neat) 1705 cm^{-1} (s, C=O), which was characterized as a 2,4-dinitrophenylhydrazone, mp 132–135 °C.

Oxidation of Methyleneadamantane with $UO_4 \cdot 4H_2O$. Methyleneadamantane (0.74 g, 0.005 mol) was oxidized with 1.7 g (0.005 mol) of $UO_4 \cdot 4H_2O$ by method B. 2-Adamantanone (0.36 g; 48% yield) was recovered, IR (CCl_4) 1715 cm^{-1} (s, C=O) (lit. 1717 cm^{-1} (s, C=O)).

Oxidation of Chalcone with $UO_4 \cdot 4H_2O$. Chalcone (2.08 g, 0.01 mol) was oxidized according to method B. A mixture (1.2 g; 50% yield) of products was isolated. An ethereal solution of the mixture was extracted with aqueous base to yield on reacidification and extraction 0.91 g (89% of product) of benzoic acid: IR (CCl_4) 1690 (C=O) and 3440 (OH) cm^{-1}: mp 121 °C (lit. mp 122 °C). Evaporation of the dried ethereal solution yielded 0.11 g (11% of product) of benzaldehyde, IR (neat) 1700 cm^{-1} (s, C=O), which was characterized as a 2,4-dinitrophenylhydrazone, mp 230 °C (lit. mp 237 °C).

Oxidation of *trans*-Stilbene with $UO_4 \cdot 4H_2O$. *trans*-Stilbene (1.8 g, 0.01 mol) was oxidized according to method B. A mixture (0.69 g; 36% overall yield) of products remained following evaporation of the solvent. The material was chromatographed on adsorbent alumina with 200 mL of petroleum ether (bp 37–55 °C), 250 mL of benzene, and 250 mL of chloroform. Evaporation of the petroleum ether solution yielded 0.085 g (12% of the product) of stilbene oxide: IR 1050 cm^{-1} (s, ROR); mp 58–60 °C (lit. mp 65–67 °C). Evaporation of the benzene and chloroform solutions yielded 0.61 g (88% of the product) of benzoin: IR (CCl_4) 3460 (s, OH), 1695 cm^{-1} (s, C=O); mp 132 °C (lit. mp 134–136 °C). The identity of the product was confirmed by gas chromatography using a Perkin-Elmer model F-11 chromatograph equipped with flame ionization detector and a 17 ft × 1/8 in. column packed with 1.75% butanediol succinate on acid washed DMCS treated Chromasorb W at 130 °C and 50 psig.

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Registry No.—$UO_4 \cdot 4H_2O$, 15737-34-5; cycloheptanecarbinol, 4448-75-3; cycloheptanecarboxylic acid, 1460-16-8; cyclooctanone 2,4-dinitrophenylhydrazine, 1459-62-7.

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A New Stereoselective Route to Trisubstituted Bromo Olefins Utilizing α-Bromoalkylides Produced by Halogen–Metal Exchange

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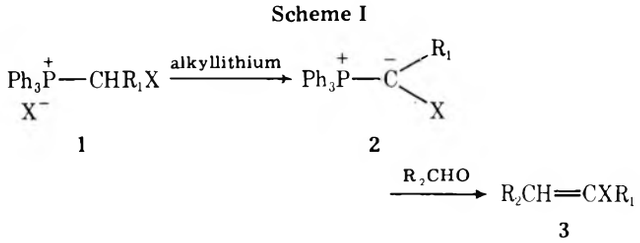
The development of general methods for the stereospecific synthesis of functionalized trisubstituted olefins has become of major importance in synthetic organic chemistry. As a new approach to the problem, the readily available triphenylphosphonium dibromomethylide has been alkylated with methyl and ethyl bromides to yield the corresponding salts **4**, which react smoothly with butyllithium at low temperature to give α-bromoalkylides **5**, formally the products of halogen–metal exchange. These ylides react with a variety of aldehydes in Wittig fashion, furnishing the corresponding trisubstituted bromo olefins **3** in yields of 30–55%. Reactions involving the ylide **5b** are usefully stereoselective, and it has been shown that in all cases it is the thermodynamically more stable isomer which predominates. In striking contrast, reactions involving the homologue **5c** are completely nonstereoselective, and this disparity appears unprecedented. Work directed toward the elucidation of the mechanisms of these processes has revealed that the detailed pathway of these reactions is determined by a number of finely balanced factors, which even a small perturbation is liable to upset. Equilibrium processes, solvent effects, and the relative thermodynamic stabilities of the resultant bromo olefins **3** all appear to exert an influence in determining reaction stereochemistry.

As synthetic intermediates, halo olefins are perhaps even more prized than their saturated counterparts. Besides being amenable to a large number of synthetic manipulations,[1] the versatile halogen grouping also permits structural elaborations in which the stereochemical relationship between other olefinic substituents often remains undisturbed.[1a-d,h,k] Consequently, a considerable effort has been devoted to the development of methods for their stereospecific synthesis.[2] In particular, the more difficult[3] stereospecific synthesis of trisubstituted halo olefins of the type RCH=CXR has aroused considerable interest (vide infra), not least because they allow ready access to a variety of trisubstituted olefins[4] which are themselves important in some areas of natural product synthesis (inter alia as intermediates in polyolefin cyclizations[5] and in insect juvenile hormone synthesis[6]).

We required a mild, unambiguous route to highly labile trisubstituted halo olefins of the above type, and an initial evaluation of existing methods pointed to the Wittig olefin synthesis[7] as a method which seemed to offer some promise. Thus, it was known that 1-bromo olefins **3a** are available from the ylide **2a**, which can be generated in the normal way from the salt **1a** as shown in Scheme I.[8] In principle therefore, the use of alkylated derivatives, e.g., **1b**, might be expected to provide an analogous route to trisubstituted bromo olefins. This hope unfortunately founders on the complete failure of standard procedures[9] for synthesizing salts such as **1b**, thus leading others[2d] to an outright dismissal of the Wittig reaction for halo olefin synthesis in which more than one carbon is required to be introduced. This impasse has, however, stimulated the development of other indirect methods based on the Wittig route. Thus, Schlosser[10] and Corey[11] have both independently shown that reaction of certain β-oxidophosphonium ylides ("betaine ylides") with various electrophilic sources of halogen does produce olefins of type **3**, although involving as it does chemical modification of a reactive intermediate, yields

Scheme I



a, R_1 = H, X = Br; b, R_1 = Me, X = Br; c, R_1 = X = H

were fair to poor and the generality of the route seems doubtful.[12]

The inspiration for the present work sprang from a key observation which had been made earlier by Köbrich.[8b] He reported that when the salt **1a** was treated with phenyllithium a diversion from the expected course ensued, and a 2:3 mixture of phosphoranes **2a** and **2c** resulted, thus demonstrating that extraction of a bromine cation from this salt competes rather effectively with the usual deprotonation pathway. He also noted that the action of butyllithium produced *exclusively* **2c**, the product of a formal metal–halogen exchange.[13]

We have developed and expanded on these observations and now wish to record a new general route to α-bromoalkylides which is based on halogen–metal exchange rather than on the usual deprotonation sequence. This not only furnishes a direct highly stereoselective route to some bromo olefins **3** but also provides further information on the stereochemistry of Wittig reactions leading to trisubstituted olefins, about which little appears to be known.

Results

Reaction of the readily available triphenylphosphonium dibromomethylide[14] with hydrogen bromide and methyl and ethyl bromides produced the known **4a**[15] and the previously unreported salts **4b** and **4c** in 86, 77, and 62% yields, respectively (Scheme II). As would be anticipated, while the reaction of hydrogen bromide with the ylide at 0 °C was instantaneous, methyl bromide reacted more slowly over about a 1-h period, the progress of reaction being usefully indicated by the gradual discharge of the red ylide color. Alkylation with ethyl bromide was very much more sluggish and required a reaction period of 24–36 h.

When **4b** was suspended in THF and treated with 1 equiv of butyllithium at −40 °C, a characteristic orange coloration developed immediately, which was discharged by bubbling hydrogen bromide through the solution. Workup of this reaction led to the isolation of salt **1b** in high yield, and in addition gas chromatographic analysis of the volatile fraction revealed butyl bromide as the only constituent besides solvent residue.

Since this result appeared to demonstrate quite convincingly that the desired halogen–metal exchange was occurring cleanly, the experiment was repeated with benzaldehyde added as an ylide trap. This reaction was detectably exothermic, even below −60 °C, and resulted again in an imme-

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Table I. Products from the Reaction of Triphenylphosphonium α-Bromoalkylides with Aldehydes

Run	Ylide	Aldehyde	Product	Yield,[a] %	Isomer distribution,[b] Z:E
1	**5b**	PhCHO	**3a**	40	>95:5[c]
2		$C_6H_{13}CHO$	**3b**	55	87:13[d]
3		t-C_4H_9CHO	**3c**	16[e]	25:75
4		MeOCH=CHCHO	**3d**	30	87:13
5	**5c**	PhCHO	**3e**	48	53:47
6		$C_6H_{13}CHO$	**3f**	55	58:42
7	**5a**	PhCHO	**3g**	44	49:51
8		t-C_4H_9CHO	**3h**	~6[e]	98:2

[a] Yields refer to distilled materials and in most cases analytically pure materials. [b] The error in the Z:E ratio is ca. ±2% when determined by integration of GLC peaks and ±5% in the NMR determination. [c] NMR determination. [d] GLC determination. [e] These reactions were very clean, and the low isolated yields are probably a reflection of the unsuitability of the isolation procedure for volatile products. No further attempt was made at optimization.

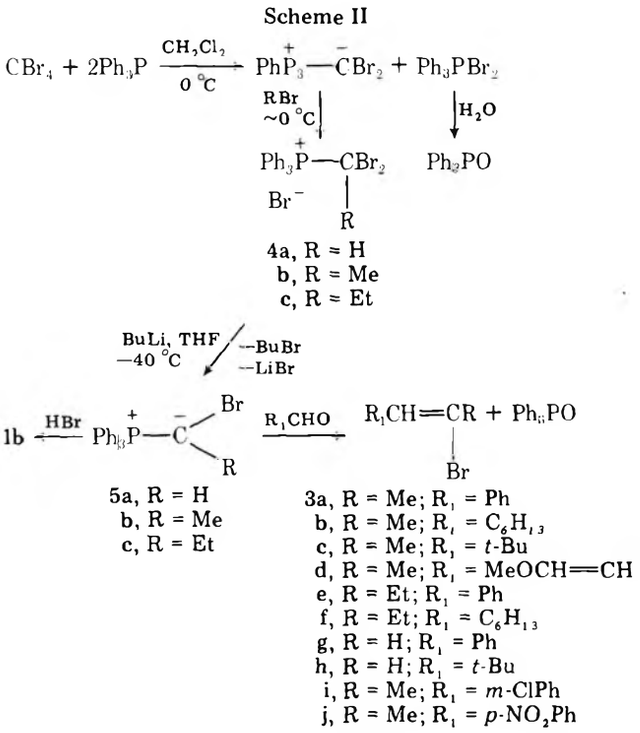
diate discharge of the color. Slow warming to room temperature followed by concentration, extraction, chromatography on silica gel, and subsequent distillation furnished pure (Z)-1-phenyl-2-bromo-1-propene in 40% yield. A similar sequence using salt **4c** produced the homologous bromo olefin in 48% yield. The scope of the new reaction was then explored using a variety of other aldehydes, and the results are summarized in Scheme II and Table I.

Configurational Assignments. The structures of the resulting bromo olefins follow from the lack of ambiguity in the synthetic method[7e] and were confimed in all cases by elemental analyses for new compounds as well as by spectral data (cf. Experimental Section). Somewhat surprisingly, a number of these simple compounds have not been previously described, and only compounds **3a**,[16] **3b**,[17] and **3g**[8] could be identified by comparison with their known spectral characteristics. For previously unknown trisubstituted bromo olefins where both isomers were clearly distinguishable in their ^1H NMR spectra, e.g., **3c, 3d,** and **3e,** a secure configurational assignment could be reached on the expectation that the vinylic proton in the E isomer, which is deshielded by the cis vicinal bromine, should resonate at lower field than in the Z isomer, where the halogen is trans. Besides the existence of another precedent which concurs with this view,[18] these assignments were confirmed in a number of cases by reduction of the bromides with sodium in liquid ammonia and subsequent gas chromatographic analysis of the derived olefins. This highly stereoselective protiodebromination reaction[19] was also used to assign configurations in cases where the NMR spectra were of little help, e.g., **3b.** Interestingly, although in the majority of cases the stereoselectivity of this reaction was around 95%, as originally claimed,[19b] with bromo diene **3d** it fell to ~85%, presumably reflecting the lesser configurational stability of pentadienylic anions vis-à-vis their allylic counterparts.

The 3-chloro- and 4-nitro-substituted derivatives **3i** and **3j** were both assigned as Z isomers on the basis of the chemical shifts of their olefinic protons, which in neither case appeared as low field as in the unsubstituted E isomer.

Since the stereochemical outcome of the new reaction has a bearing on the question of the stereochemistry and mechnism of the Wittig reaction, it was necessary to exclude the possibility of olefin stereomutation under the reaction conditions. This was ruled out by control experiments in which artificial mixtures of (Z)- and (E)-**3a** submitted to the reaction conditions were recovered unchanged and in other cases by careful assay of the diastereomeric ratio at each stage of the workup procedure.

Scheme II



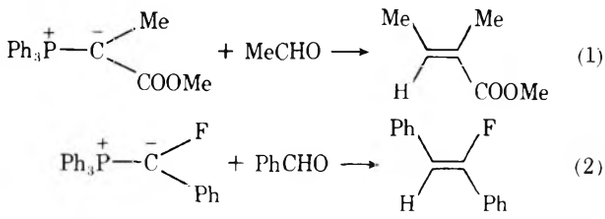
Thermodynamic Stabilities of Bromo Olefins. A prerequisite to the understanding of factors which govern the stereochemical outcome of these reactions is some information concerning the relative thermodynamic stabilities of the isomeric pairs of resultant halo olefins. In order to obtain this, each of the pairs was treated either with small amounts of HBr[20] and left to stand at room temperature for 3 weeks or refluxed with iodine in acetic acid.[21] With HBr this resulted in the pairs **3b** and **3d** becoming richer in the Z diastereomer to the extent of about 10%, while in **3c** the opposite shift occurred and the proportion of this isomer fell by a similar amount. Bromides **3a** and **3e,** each initially present in about 1:1 isomeric ratios, were not readily isomerized by acid, each mixture becoming enriched in the Z isomer by only a few per cent. However, pure (Z)-**3a** remained *completely* unaffected by this treatment and also by iodine in acetic acid. Use of the latter reagent with the pair **3c** resulted in quantitative conversion to the E isomer.

Thus, it seems reasonable to conclude that generally Z isomers are more stable, and this is in essential agreement with earlier findings for other trisubstituted halo olefins where it has been found that the lowest energy configuration is obtained in situations where the halogen and proton groupings are in a trans relationship to each other.[20] The one exception to this in the present case is the pair **3c** where the steric bulk of the *tert*-butyl group apparently reverses the normal order. Interestingly, heat of formation estimates based on additivity of group properties[22] predict that Z isomers should be favored by 1.0 kcal/mol.

Discussion

The new reaction constitutes a general procedure for the transformation of an aldehyde function to a trisubstituted bromo olefin and should be of great value in synthesis. For example, **3b,** an important intermediate in the synthesis of the fragrant components of cassia oil which was previously made from heptanal in three steps,[17] is now directly available from the same starting material. In addition, the mildness of the method makes it ideally suited for the synthesis of labile bromo olefins: **3d** fumed in moist air and would seem to be a

Scheme III



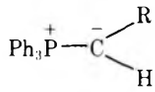
good example of a molecule whose unambiguous construction by such simple means makes the method especially attractive. The one factor which will limit the general applicability of the route is the electrophilicity of the alkylation reagent used to prepare the salts 4 (RBr in Scheme II). The practical limits of alkylating the rather stable triphenylphosphonium dibromomethylide by using simple alkyl halides as electrophiles are probably already reached at ethyl bromide. However, it is likely that other reactive halides such as allyl and benzyl[15a] derivatives might be useful in providing further extensions and possibilities.

The key halogen–metal exchange between the salts 4 and butyllithium appears to be strikingly clean, and possible complications such as competitive reaction of the alkyllithium with the α-bromoalkylide or its alkylation by the concomitantly produced butyl bromide do not seem to be a problem at −40 °C. Remarkably, the preference for bromine abstraction over deprotonation is so overwhelming that it even occurs in the salt **4a**, where the acidity of the proton must be considerably enhanced. When this salt was used as the ylide precursor and benzaldehyde as the carbonyl component, β,β-dibromostyrene was produced as an impurity to an extent of <2%, thus making this a viable alternative route for 1-bromo olefin synthesis. The origin of this effect is presumably kinetic, and parallels exist[23] in the similar behavior of some bromo alkanes and bromo olefins with butyllithium. In these cases, halogen–metal exchange proceeds several orders of magnitude faster than the corresponding proton–metal exchange and can provide a useful route to thermolabile lithium carbenoids.[23b]

The remainder of the reaction sequence, viz., reaction of α-bromoalkylides with aldehydes, is noteworthy in the provision of an unprecedented disparity between the highly stereoselective **5b** and the unselective homologue **5c**. In this case, the usual trend[7d] whereby unbranched homologues react with *greater* stereoselectivity is completely reversed.

Stereochemistry and Mechanism. The mechanism of the Wittig olefin synthesis has been the subject of a considerable body of work[24–26] which has resulted in a better understanding of the mechanism(s) of those processes which lead to 1,2-disubstituted olefins; although, there is still uncertainty over the exact nature of the intermediate(s)[27] which may or may not be involved. In turn, the pathways of unmodified[28] Wittig reactions producing trisubstituted olefins remain completely in the dark, and only a few scattered observations appear to be available. For example, the stereochemical outcome of the reactions shown in Scheme III[29] has been rationalized on the basis that steric hindrance to resonance is minimized in the products obtained. However, examples like these probably cannot be claimed as typical since the double bond is substituted by at least one strongly conjugating group, the result of which may well be to so inflate factors of thermodynamic preference that other considerations which may normally play a part are thrust into the background.

A starting point for the rationalizations collated and discussed by Schlosser to explain the stereochemical outcome of reactions leading to 1,2-disubstituted olefins was an initial classification[7d] of the ylide as "reactive", "moderated", or "stable", as determined by the nature of the substituent at the ylide carbon. This classification has very important consequences for the energetics of the initial addition step of the ylide with carbonyl compounds, directly affecting the equilibrium constant for this process which connects ylide and carbonyl starting materials with betaine or oxaphosphetane intermediates. This equilibrium constant apparently dominates the stereochemical control of the resultant olefin by its regulation of the *reversibility factor*[7d] of the initial addition, which in turn is held to be indirectly responsible for the production of largely trans olefins from stable ylides and to some extent from moderated ylides, for cis olefins from reactive ylides under conditions of kinetic control ("salt-free" conditions), and for the preponderance of trans olefins from the same ylides under equilibrium conditions. While stable ylides, e.g., **6a**, characterized by extensive delocalization of negative



6a, R = COOR
b, R = alkyl
c, R = aryl or alkenyl

charge onto a substituent, are often isolable and usually require heating to effect reaction, reactive ylides, e.g., **6b**, are labile transients invariably reacting with release of energy, and reactions are often carried out at low temperatures. In these cases, the saturated aliphatic substituent strongly increases ylide basicity and hence reactivity. Between these two extremes a third class of moderated ylides has been recognized, where, due to the relatively less effective delocalizing ability of the substituent, e.g., **6c**, the addition step is usually accompanied by rather small energy changes. Turning to the present case, although Schlosser[25b] has also exemplified the latter group by triphenylphosphonium chloromethylide,[30] a priori it is not clear how far the stabilizing features of the bromine substituent,[31] viz., its electronegativity and vacant 4d orbitals, will be opposed by the destabilizing influence of the alkyl group. In any event, the experimental observation of an energy releasing initial step immediately suggests that these phosphoranes possess some characteristics of reactive ylides.

The question of the operation of equilibria processes in these systems was probed by runs 3 and 6 in Table II. Table II also contains the results of other experiments which were carried out in an effort to gain some information in regard to factors controlling the reaction stereochemistry. These crossover experiments, essentially the classical test[25a] for the operation of the *reversibility factor*, demonstrate quite conclusively that the initial addition step is reversible for ylide **5b** and, to within the limits of experimental detection, irreversible for **5c**. This result is also consonant with the differing stabilities of their derived intermediates. While the intermediates from **5b** were observed to decompose to olefin and phosphine oxide between 5–15 °C, those originating from **5c** were much less stable, decomposing at about −25 °C. These results are significant, and taken together they suggest that important differences exist between the relative free energies of intermediates lying along the respective reaction coordinates. Stereoselectivity is often reduced by the use of more electrophilic aldehydes; run 4 shows that in this case the selectivity of **5b** remains unimpaired. Thus, although both ylides appear to be more reactive than moderated, reversibility may well be important in reactions of **5b**, particularly in the presence of salts.

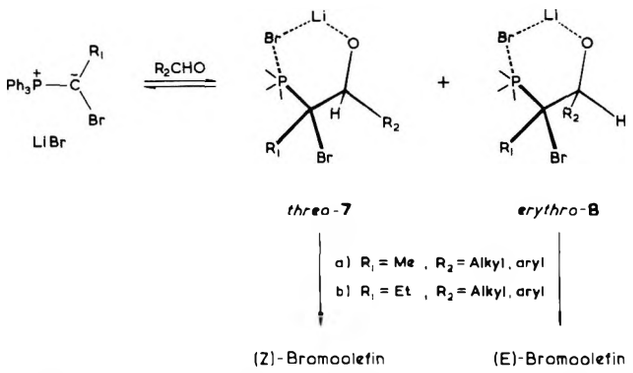
Salt effects are known to have quite dramatic consequences on the stereochemistry of Wittig reactions,[26] and indeed the lithium bromide which is generated unavoidably with these ylides appears to be intimately involved in their reactions. This can be inferred from run 5 (Table II) where DMF, which

Table II. Effect of Reaction Conditions on Bromo Olefin Stereochemistry

Run	Ylide–aldehyde	Solvent	Reaction temp,[a] time	Product	Isomer distribution, *Z*:*E*
1	**5b**–PhCHO	THF	20 °C, 5 min	**3a**[c]	>95:5[c]
2			−55 °C, 22 h	**3a**	>95:5
3			*b*	**3a** + **3i**	94:6[d]
					>95:5
4	**5b**–*p*-NO_2PhCHO	THF	Standard[g]	**3j**	>95:5[c]
5	**5b**–PhCHO	DMF[e]	−50 °C, 10 min	**3a**	57:43
6	**5c**–PhCHO	THF	As for run 3	**3e**	53:47[f] (>99%)

[a] Ylide generation was initially carried out at −40 °C in all cases except run 5, where −25 °C was used due to the sluggishness of reaction at −40 °C. [b] At −55 °C, 70 min; then add 1 equiv of *m*-ClPhCHO; −60 °C, 120 min. [c] NMR determination. [d] Combined GC–MS analysis. [e] Reaction in this solvent gave very poor yields of bromo olefin (cf. footnote *a* also); THF is the solvent of choice. [f] GLC determination. [g] See Experimental Section.

Scheme IV



is known to mimic salt-free conditions,[26] is seen to have a decisive influence on reaction stereochemistry. In this medium the stereoselectivity of **5b** is completely lost. This result appears to argue against direct oxaphosphetane formation in these systems in other solvents and points instead to the initial formation of a lithium bromide complexed betaine, as represented perhaps by **7** or **8** in Scheme IV.

Finally, the normal stereoselectivity of **5b** together with the results from the investigation of the relative thermodynamic stabilities of the resultant bromo olefins raise the question of the importance of aspects of thermodynamic control in these processes. Apparently, in cases where there is a thermodynamic preference for one particular isomer, that isomer always predominates. This is particularly emphasized by the contrast between the isomer distribution in runs 2 and 3 (Table I), where a reversal in the general trend of thermodynamic preference is nicely paralleled by a corresponding reversal in isomer distribution.

Bearing the above discussion in mind, a tentative but not unreasonable interpretation of these reactions is given in Scheme IV.

If addition occurs to give initially both the threo and erythro lithium bromide complexed betaines (Sheme IV), then a situation of thermodynamic control can be envisaged where *threo*-**7** is preferentially consumed because it leads to the more stable olefin, usually the *Z* isomer, through a lower energy transition state. In the case of ylide **5b**, as a consequence of the mobile equilibrium with starting materials, the concentration of **7a** is continually replenished at the expense of **8a** and high stereoselectivity then results. Conversely, since systems involving the homologue **5c** lack demonstrable equilibria processes, kinetic control prevails and these reactions are devoid of stereoselectivity. Of course, in salt-free reactions the energies of the uncomplexed betaines are presumably increased, and this no doubt prevents the occurrence of equilibria processes, resulting in a loss of stereospecificity. Similar results which are also in keeping with this suggestion have been obtained with other moderated ylides.[26]

Scheme IV accounts quite well for all of the major features of these reactions, but the question as to why the introduction of a small β alkyl grouping results in such a profound change is not answerable with any certainty. Clearly, the detailed pathway of these reactions is determined by a number of finely balanced factors, which even a small perturbation is liable to upset.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz with a Hitachi Perkin-Elmer R-20B instrument (tetramethylsilane as an internal standard; $CDCl_3$ solvent unless stated otherwise). IR spectra were obtained with a Beckmann IR 4240 instrument for liquid film samples. UV spectra were taken on a Varian Techtron Model 635 instrument in cyclohexane solvent unless stated otherwise. Mass spectra and combined GC–MS analyses were taken at 70 eV with an AEI MS 3074 double beam instrument fitted with a Pye Unicam Series 104 gas chromatograph unit. Analytical GLC was performed on a Varian Aerograph Series 1800 preparative instrument: column A, 5 ft × 0.25 in, 5% SE 30 on Chromosorb W; column B, 10 ft × 0.25 in, 10% SE 30 on Chromosorb W (See Table III). Elemental analyses were performed by the Australian Microanalytical Service, CSIRO, Victoria, Aust.

Materials. Triphenylphosphine was used as supplied, and carbon tetrabromide was purified[32] by passage through an alumina column using dichloromethane as solvent. Dichloromethane was purified by shaking industrial grade material successively with 5% sodium carbonate and water, followed by drying quickly over calcium chloride. Decantation onto freshly activated calcium chloride,[33] stirring overnight, decantation again, and fractionation gave a material (bp 40 °C) which was stored over 4A molecular sieves. Tetrahydrofuran was purified by initial refluxing and distillation from cuprous chloride to remove traces of peroxides, stirring overnight with 5% w/v calcium hydride,[33] and subsequent fractionation (bp 66–67 °C). It was stored over 4A molecular sieves in a dark bottle using a nitrogen atmosphere. Benzaldehyde, 3-chlorobenzaldehyde, pivalaldehyde, and heptanal were used as freshly distilled commercial samples. 3-Methoxy-2-propenal was synthesized as reported below, and 4-nitrobenzaldehyde was used as supplied.

Synthesis of Triphenylphosphonium Salts 4b and 4c. The procedure used for the synthesis of 1,1-dibromoethyltriphenylphosphonium bromide (**4b**) serves as an example. A 2-L three-neck flask equipped with a pressure equalized dropping funnel, mechanical stirrer, and low temperature thermometer was flamed and then allowed to cool while a slow current of dry oxygen-free nitrogen was passed through the apparatus, this flow being maintained throughout the preparation. When cool, the flask was charged with purified[32] carbon tetrabromide (99.6 g, 0.30 mol) in pure dry dichloromethane (300 mL) and the dropping funnel with triphenylphosphine (157.2 g, 0.60 mol) in dichloromethane (300 mL). After cooling to −5–0 °C, the solution of triphenylphosphine was added over about 10–15 min with rapid stirring. Stirring was continued for 10–15 min after the addition was complete, during which time a heavy precipitate appeared in the orange-red solution of triphenylphosphonium dibromomethylide.

The dropping funnel was then removed, and a U-shaped tube was fitted into the flask, a long arm of which was adjusted through a screw cap fitting so that it dipped below the surface of the ylide solution. The other end was fitted through an adaptor to a cold flask containing methyl bromide (38.0 g, 0.40 mol), and the nitrogen flow was then redirected to pass through the tube from the adaptor which was also

Table III. Selected Properties of Bromo Olefin Products

Compd	GLC data[a] Column [temp (°C)]	R_t, min[b] Z	E	Analytical data Found, % C	H	Br	Formula	Required, % C	H	Br
3b	A [75]	13.6	15.9				[c]			
3c	B [100]	14.5	17.5	50.87	8.31	39.1	$C_7H_{13}Br$	47.48	7.40	45.12
3d	B [140]	11.4	12.5	40.91	5.37	44.8	C_6H_9BrO	40.71	5.12	45.13
3e	A [90]	10.6	12.4	56.30	5.19	38.8	$C_{10}H_{11}Br$	56.90	5.25	37.85
3f	B [150]	23.4	25.5	54.45	8.50	36.40	$C_{10}H_{19}Br$	54.80	8.74	36.46
3g	B [130]	10.8	8.0				[d]			
3h	B [170]	12.8	10.1				[e]			
3i	A [100]	13.8		47.13	3.55	35.0	C_9H_8BrCl	46.69	3.48	34.51

[a] Nitrogen flow rates: column A, 150 mL/min; column B, 80 mL/min. [b] Related *Z* chloro olefins are also invariably more volatile than the *E* isomers; see ref 19a. [c] Previously described in ref 17. [d] Previously described in ref 8. [e] *E* isomer previously described in ref 36.

fitted with a gas inlet facility. With occasional dry ice cooling to keep the temperature of the ylide solution at ~0–3 °C, the methyl bromide was slowly vaporized into the gently stirred ylide solution, which decolorized completely in 60–90 min. Workup was carried out by warming to room temperature, adding 500 mL of saturated aqueous sodium bicarbonate solution (1.3 M, 0.65 mol) with vigorous stirring, separating the pale yellow organic solution, drying ($MgSO_4$), and distilling off the solvent. Removal of the last traces of solvent on a rotary evaporator gave a solid which was triturated with benzene by high speed stirring to separate the soluble triphenylphosphine oxide from the insoluble white salt. Filtration and air drying gave 141 g (89%) of the crude material, mp 191–193 °C. Purification was effected by dissolution in a minimum volume of hot dichloromethane and reprecipitation with hot acetone. Filtration followed by drying in a vacuum oven for 16 h at 80 °C gave 122 g (77%) of material, mp 198–201 °C dec. An analytical sample had mp 201–202 °C dec; ^1H NMR δ 3.02 (3 H, d, J = 15.6 Hz), 7.50–8.20 (m, 15 H). Anal. Calcd for $C_{20}H_{18}Br_3P$: C, 45.41; H, 3.43; Br, 45.32. Found: C, 45.43; H, 3.43; Br, 45.3.

1,1-Dibromopropyltriphenylphosphonium bromide was obtained similarly in 62% yield except that a fourfold molar excess of ethyl bromide over the ylide was used and a reaction period of 24–36 h at 0 °C was necessary. This reaction is not complete until the color has faded *at least* to a light yellow. The material obtained from the synthesis had mp 175–177 °C. An analytical sample melted at 196–200 °C; ^1H NMR δ 1.51 (3 H, t, J = 6.2 Hz), 2.71 (m, 2 H), 7.50–8.20 (m, 15 H). Anal. Calcd for $C_{21}H_{20}Br_3P$: C, 54.80; H, 8.74; Br, 36.46. Found: C, 54.45; H, 8.50; Br, 36.4.

1-Bromoethyltriphenylphosphonium bromide (**1b**) was obtained via the reaction of triphenylphosphonium α-bromoethylide with HBr, mp 202–204 °C. Anal. Calcd for $C_{20}H_{19}Br_2P$: C, 53.36; H, 4.25; Br, 35.50. Found: C, 53.07; H, 4.45; Br, 35.1.

3-Methoxypropenal. This previously unknown aldehyde was prepared by modification of an existing procedure.[34] 1,1,3,3-Tetraethoxypropane (44 g, 0.20 mol) was stirred rapidly at room temperature with hydrobromic acid (23 mL of ~8.8 M aqueous solution, ~0.20 mol) in water (30 mL), and after 5–10 min a yellow homogeneous solution was obtained. This was added dropwise to a cold (−40 °C) well-stirred solution of sodium methoxide (0.42 mol) in methanol (200 mL), resulting in a yellow solution which was warmed to room temperature and concentrated on a rotary evaporator at 50–60 °C. Addition of acetone (150 mL) and trituration by rapid stirring resulted in the quantitative precipitation of the sodium salt of malondialdehyde as an orange solid which was dried in a vacuum oven at 55 °C for 16 h. This salt was suspended in dry diethyl ether (100 mL) and treated with methyl chloroformate (18.9 g, 0.20 mol) with rapid stirring at room temperature for 3 h, during which time the color of the salt suspension noticeably lightened to a creamy white and the reaction vessel became warm. Filtration and removal of the volatiles on a rotary evaporator furnished the methylvinyl carbonate as a labile low melting solid, which was immediately dissolved in dry dichloromethane (~100 mL) and decomposed with ~1 g of *p*-toluenesulfonic acid. When CO_2 evolution had ceased, careful removal of dichloromethane on a rotary evaporator followed by distillation yielded 8.2 g (48%) of 3-methoxypropenal, bp 47–48 °C (5 mmHg). This aldehyde is indefinitely stable if kept in a freezer compartment well below its melting point (~25 °C), but it rapidly polymerizes on standing at room temperature: ^1H NMR δ 3.78 (3 H, s), 5.56 (1 H, dd, J = 8.4 Hz), 7.46 (1 H, d, J = 12.5 Hz), 9.36 (1 H, J = 8.4 Hz); UV λ_{max} 233 nm (ε 54 500), 312 (600); *m/e* 86, 85, 71, 57, 54.

Procedure for Wittig Reactions. The reaction leading to bromo diene **3d** serves as an example. The usual setup for reactions involving reactive phosphoranes was employed; i.e., a three-neck flask was fitted with a pressure equalized dropping funnel, mechanical stirrer, and low temperature thermometer and was arranged such that a slow flow of dry deoxygenated nitrogen could be maintained throughout the procedure. After flaming and cooling, the flask was charged with 1,1-dibromoethyltriphenylphosphonium bromide (16.9 g, 32.0 mmol) suspended in THF (60 mL). A convenient way of pulverizing the salts without danger of their concomitant hydration consisted of simply stirring the salt suspension gently for 20–30 min; this ensured that extremely fine particles resulted. The dropping funnel was then filled with butyllithium (25 mL of a 1.16 M solution in hexane, 29.0 mmol)[35] from a nitrogen-filled volumetric pipet, and the reaction vessel was cooled to −40 °C in a dry ice–acetone bath. Butyllithium was then added dropwise with stirring over about 10–15 min, the internal temperature being carefully regulated between −40 to −45 °C. After complete addition, the walls of the dropping funnel were rinsed with 4–5 mL of dry hexane, and stirring was continued at −40 °C for 10 min to ensure complete consumption of butyllithium, which was often indicated by a dramatic color change from blood-red to tangerine-orange, depending on the rate of addition of butyllithium (it is of the *utmost importance* to the yields obtained that the carbonyl compound *not* be added until it is certain that the color is a definite bright orange). 3-Methoxypropenal (2.5 g, 29.0 mmol) in THF (5 mL) was then added dropwise to the ylide solution at ~−60 °C, whereupon an exothermic reaction occurred and the color was discharged immediately to a creamy yellow. After stirring further for 10 min, warming to room temperature and filtration produced a yellowish-orange solution which after evaporation on a rotary evaporator, trituration with hexane (75 mL) by high speed stirring, filtration again, and concentration (~20 mL) was carefully column chromatographed on silica gel using hexane as eluent. Removal of the solvent gave a colorless oil which was distilled without delay in a semimicro apparatus fitted with a vacuum-jacketed Vigreux column to give 1-methoxy-4-bromo-1,3-pentadiene (1.54 g, 30%), bp 59–60.5 °C (5 mmHg). The diene was fairly stable if kept in the freezer compartment of a refrigerator, but it fumed in moist air with rapid darkening: ^1H NMR of (*Z*)-**3d**, δ 2.29 (3 H, m), 3.59 (3 H, s), 5.61 (1 H, dd, J = 10.1 Hz), 6.07 (1 H, dq, J = 10.1 Hz, $J_{allylic} \approx 1$ Hz), 6.67 (1 H, d, J = 12.3 Hz); ^1H NMR of (*E*)-**3d**, δ 2.23 (3 H, m), 3.63 (3 H, s), 5.22 (1 H, dd, J = 11.3 Hz), 6.53 (1 H, dq, J = 11.3 Hz, $J_{allylic} \approx 1$ Hz), 6.67 (1 H, J = 12.3 Hz); λ_{max} 245 nm (ε 36 000); ν_{max} 1610, 1650, 3025, 3075 cm^{-1}; *m/e* 178, 176, 163, 161, 135, 133, 97.

Similarly, the known bromo olefins 3a and **3g** (from salt **4a**) were obtained, as well as the following.

2-Bromo-4,4-dimethyl-2-pentene (3c): Bp 65–67 °C (32 mmHg); ^1H NMR of the *Z* isomer, δ 1.17 (9 H, s), 2.22 (3 H, d, $J_{allylic}$ = 1.4 Hz), 5.73 (1 H, q, $J_{allylic}$ = 1.4 Hz); ^1H NMR of the *E* isomer, δ 1.12 (9 H, s), 2.30 (3 H, d, $J_{allylic}$ = 1.4 Hz), 5.86 (1 H, q, $J_{allylic}$ = 1.4 Hz); IR ν_{max} 1365, 1380, 1645 cm^{-1}.

1-Phenyl-2-bromo-1-butene (3e): Bp 59–62 °C (~0.2 mmHg); ^1H NMR of the *Z* isomer, δ 1.18 (3 H, t, J = 7.5 Hz), 2.58 (2 H, q, J = 7.5 Hz), 6.65 (1 H, bs), 7.1–7.6 (5 H, m). ^1H NMR of the *E* isomer, δ 1.18 (3 H, t, J = 7.5 Hz), 2.58 (2 H, q, J = 7.5 Hz), 6.88 (1 H, bs), 7.1–7.6 (5 H, m).

3-Bromo-3-decene (3f): Bp 68–70 °C (2 mmHg); ^1H NMR of the *Z* isomer, δ 0.70–1.50 (11 H, m), 1.07 (3 H, t, J = 7.5 Hz), 2.05 (2 H, m), 2.41 (2 H, bq), 5.59 (1 H, t, J = 7.2 Hz, $J_{allylic}$ = 1.1 Hz); ^1H NMR of the *E* isomer, δ 0.70–1.50 (11 H, m), 1.07 (3 H, t, J = 7.5 Hz), 2.05 (2 H, m), 2.41 (2 H, bq), 5.77 (1 H, t, J = 7.6 Hz, $J_{allylic}$ < 1.0 Hz); IR ν_{max} 1635 cm^{-1}.

(*Z*)-1-Bromo-3,3-dimethyl-1-butene (3h). Although the *E* isomer is known,[36] the *Z* isomers is not known: ^{1}H NMR δ 1.2 (9 H, s), 6.08 (1 H, d, J = 3.1 Hz), 6.09 (1 H, d, J = 3.1 Hz); IR ν_{max} 730, 1630 cm^{-1}.

(*Z*)-1-(3-Chlorophenyl)-2-bromo-1-propene (3i): Bp 76–78 °C (~0.02 mmHg); ^{1}H NMR δ 2.28 (3 H, d, J = 1.3 Hz), 6.38 (1 H, bs), 6.90–7.40 (5 H, m); IR ν_{max} 1090, 1570, 1600, 1650 cm^{-1}.

(*Z*)-1-(4-Nitrophenyl)-2-bromo-1-propene (3j): Mp 82–84 °C (recrystallized from hexane); ^{1}H NMR δ 2.52 (3 H, d, J = 1.3 Hz), 6.78 (1 H, bs), 7.69 (2 H, m), 8.21 (2 H, m); IR ν_{max} 1340, 1530, 1570, 1600, 1630 cm^{-1}. For other properties of the bromo olefins, see Table III.

Bromo Olefin Protiodebromination. The standard procedure previously described[19] for protiodechlorination was followed. To a well-stirred solution of sodium (1.8 g, 78 mg-atom) in liquid ammonia (ca. 30 mL) was added dropwise 1-methoxy-4-bromo-1,3-pentadiene (2.3 g, 13 mmol) as an 87:13 mixture of *E,Z* and *E,E* isomers, respectively, in hexane (5 mL). After stirring for 5 min, the excess sodium was neutralized with solid ammonium chloride, the ammonia was evaporated, and water (30 mL) and hexane (30 mL) were added. After extraction and washing with water and subsequently with 2% H_2SO_4 and dilute sodium bicarbonate, the organic layer was dried ($CaCl_2$) and the hexane carefully removed at atmospheric pressure, leaving 1-methoxy-1,3-pentadiene[37] (~0.80 g, 66%) as a 73:27 mixture of *E,E* and *E,Z* diastereomers, respectively. The major isomer was confirmed by matching its NMR and UV spectra with those of the known compound.[37]

This sequence was also successful for the assignment of (*Z*)-2-bromo-2-nonene (**3b**) but failed for those bromo olefins containing an aromatic ring, e.g., **3a**. In these cases, the derived olefins appeared to undergo further polymerization, presumably induced by sodium amide, which is a well-known process for styrenes.

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Registry No.—**1b**, 66070-22-2; (*Z*)-**3a**, 21453-89-4; (*E*)-**3a**, 54624-37-2; (*Z*)-**3b**, 24404-60-2; (*E*)-**3b**, 66070-23-3; (*Z*)-**3c**, 66070-24-4; (*E*)-**3c**, 66070-25-5; (*E,Z*)-**3d**, 66070-26-6; (*E,E*)-**3d**, 66070-27-7; (*Z*)-**3e**, 66070-28-8; (*E*)-**3e**, 66070-29-9; (*Z*)-**3f**, 66070-30-2; (*E*)-**3f**, 66070-31-3; (*Z*)-**3g**, 588-73-8; (*E*)-**3g**, 588-72-7; (*Z*)-**3h**, 66070-32-4; (*E*)-**3h**, 38203-90-6; (*Z*)-**3i**, 66070-33-5; (*E*)-**3i**, 66070-34-6; (*Z*)-**3j**; 38319-07-2; (*E*)-**3j**, 38319-08-3; **4a**, 56506-90-2; **4b**, 66070-35-7; **4c**, 66070-36-8; **5a**, 66070-37-9; **5a** uncharged isomer, 39598-55-5; **5b**, 66070-38-0; **5b** uncharged isomer, 66070-39-1; **5c**, 66070-40-4; **5c** uncharged isomer, 66070-41-5; PhCHO, 100-52-7; $C_6H_{13}CHO$, 111-71-7; *t*-C_4H_9CHO, 630-19-3; MeOCH=CHCHO, 4652-35-1; *p*-NO_2PhCHO, 555-16-8; triphenylphosphonium dibromomethylide, 66070-42-6; triphenyldibromomethylenephosphorane, 42867-45-8; 1,1,3,3-tetraethoxypropane, 122-31-6; malondialdehyde sodium salt, 24382-04-5.

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Preparation and Photochemistry of Cyclohexene-1-carbonitriles

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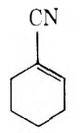
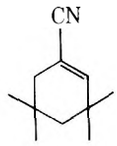
Irradiation of cyclohexene-1-carbonitriles with the full arc of a Hanovia 450-W lamp gives bicyclo[3.1.0]hexane-1-carbonitriles. Specifically, cyclohexene-1-carbonitrile gives bicyclo[3.1.0]hexane-1-carbonitrile and bicyclo[3.1.0]-hexane-6-carbonitrile. Similar irradiation of 3,3,5,5-tetramethylcyclohexene-1-carbonitrile gives rise to 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile and 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile. The structures were assigned on the basis of synthesis and NMR spectroscopy. The nitriles for irradiation were synthesized from the appropriate ketones. Cyclohexene-1-carbonitrile was prepared by dehydration of the cyanohydrin of cyclohexanone. 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile was prepared from 3,3,5,5-tetramethylcyclohexanone by conversion to the corresponding vinyl chloride followed by treatment with cuprous cyanide. In the photolysis, significant amounts of unsaturated nitriles are sometimes formed, but they have not been characterized since they are photolabile and their yields are variable.

In this paper, we report the synthesis of two cyclohexene-1-carbonitriles, their photochemistry, and the identification of the photolysis products. The study is restricted at present to two substrates, **1** and **2**.



1



2

Results

Synthesis of Cyanocyclohexenes, 1 and 2. Nitrile **1** was prepared from cyclohexanone cyanohydrin as described in the literature.[1]

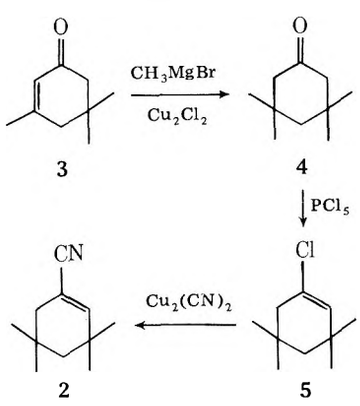
The tetramethyl derivative **2** could not be obtained in such a straightforward manner from ketone **4**, since the equilibrium constant for cyanohydrin formation is unfavorable.[2a] The compound was obtained as depicted in Chart I, using isophorone as a starting point.[2b]

Photolysis of Cyanocyclohexenes, 1 and 2. The solvent for these irradiations was hexane, which had been treated with fuming sulfuric acid to remove absorbing impurities. This was necessary because of the low intensity, short wavelength absorption of the acrylonitrile derivatives. For example, acrylonitrile has an absorption maximum (EtOH) at 215.5 nm, log ϵ 1.69.[3]

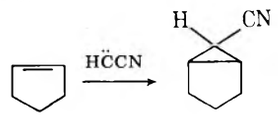
Irradiation of a $\sim 10^{-2}$ M solution of cyanocyclohexene **1** with the full arc (quartz) of the Hanovia 450-W medium pressure mercury lamp gave rise to two products. The reaction progress was monitored by VPC analysis. The irradiation was continued for 24 h. The products were separated by preparative VPC.

The NMR spectra were not particularly informative, but they showed no resonances in the vinyl region (δ 5–7). The structures were proved by unambiguous synthesis after the tentative structures **6** and **7** had been assigned.

Chart I

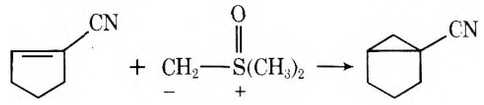


Compound **6** was prepared by reaction of cyclopentene with cyanocarbene,[4,5] which gave an oil identical with one of the photoproducts according to VPC, NMR, and infrared spectral comparison. Both the synthesis and photolysis gave mixtures of the epimers of **6**.



6

The second product (**7**) of the rearrangement of 1-cyanocyclohexene was synthesized from 1-cyanocyclopentene by treatment with dimethyloxosulfonium methylide, as described by Corey and Chaykovsky.[6]

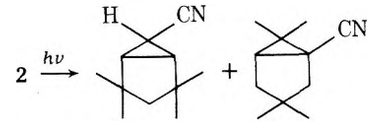


7

Compound **7** synthesized this way was identical in all respects with one of the above photoproducts. However, the synthesis was not without some difficulties. The cyanocyclopentene was obtained pure only after treatment with *tert*-butoxide. A chlorine-containing impurity is apparently formed when the cyanohydrin of cyclopentanone is dehydrated with phosphorus oxychloride–pyridine. However, the material shown to be present by VPC was not identified, but its mass spectrum showed a parent ion at *m/e* 129, with the isotope distribution of a single chlorine atom. In the synthesis of **7**, a poor yield (15%) of the required compound was obtained. The product was not contaminated with other volatile compounds, and the balance of material was water soluble. The water-soluble substance was not investigated.

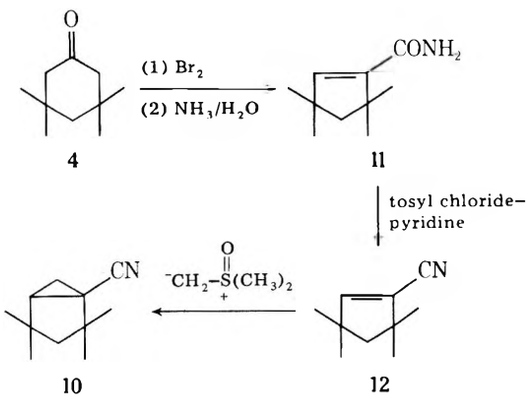
Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. This nitrile was irradiated with the Hanovia 450-W mercury lamp as described above. After 24 h, two components were observed (ratio 4:1, by VPC). The products were isolated as described in the Experimental Section.

The minor product was identified from its 220-MHz NMR spectrum, which indicated the structure 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile (**8**).



8 **9**

Chart II



The NMR spectrum of **8** is simple owing to the symmetry of the molecule. Resonances appeared at δ 0.86 and 1.28 (each 1 H, d, J = 14.0 Hz, ring CH_2), 1.01 [1 H, t, J = 3.5 Hz, C(CN)H, partially obscured by a Me signal], 1.02 and 1.21 (each 6 H, s, Me), and 1.77 (2 H, t, bridgehead CH).

Interpretation of the NMR spectrum of **9** was not so straightforward. The gross features of the spectrum were consistent with structure **9**. The spectrum, 220 MHz, showed resonances at δ 0.98, 1.06, 1.17, and 1.31 (all 3 H, s, Me). A doublet of doublets (J = 4.0 and 8.0 Hz) at δ 1.94, is assigned to the bridgehead, cyclopropyl methine proton. The methylene group vicinal to the nitrile function showed an AB quartet (centered at δ 1.75 and 1.5, respectively, with J = 12.0 Hz). The lower field doublet showed a further, long-range splitting of 2.0 Hz. One resonance showed complex splitting (δ 1.64) and is assigned to one methylene group proton, vicinal to the bridgehead methine. The second proton of this methylene group is obscured by the methyl group signals.

Although the spectra of **9** support this structure, it was not possible from the spectra alone to rule out the alternative structure, 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (**10**).

Thus, to verify the structural assignment, a sample of **10** was synthesized as shown in Chart II, and the spectra were compared with those of the photoproduct.

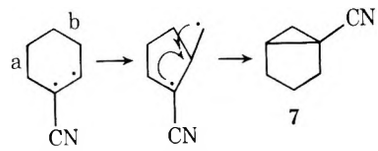
The ketone **4** was converted to the known[7] amide **11**, which was dehydrated to afford the nitrile **12**. The latter on treatment with dimethyloxosulfonium methylide gave **10**.

The VPC behavior and NMR spectrum of **10** were different from those of the photoproduct **9**. In the 220-MHz NMR spectrum, the resonance furthest downfield (δ 1.88) was a doublet of doublets (J = 6.0 and 4.0 Hz), and is assigned to the bridgehead methine proton of the cyclopropyl ring. The spectrum showed four 3-proton resonances at δ 0.98, 1.10, 1.27, and 1.40. Resonances attributed to the AB system associated with the methylene group flanked by the two *gem*-dimethyl groups were also observed, interspersed with the methyl group resonances. Thus, the spectrum is similar to that of the major photoproduct from the photolysis of nitrile **9**, but the spectra are not identical. Also, the retention times of the two compounds (photoproduct and synthetic) are different on VPC. Thus, we can confidently assign structure **9** to the photolysis product.

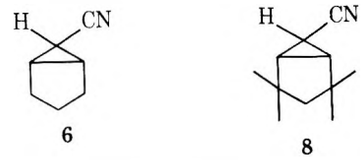
Discussion

Even though the light output is low in the region of their absorption, the cyclohexene-1-carbonitriles **1** and **2** rearrange to bicyclo[3.1.0]hexanecarbonitriles on irradiation with a medium-pressure mercury lamp. The reaction formally resembles the "type A" rearrangement of enones,[8] in that a vinyl group is converted to a cyclopropyl moiety. (We note that rearrangements have been observed in the photochemistry of dinitriles.[9])

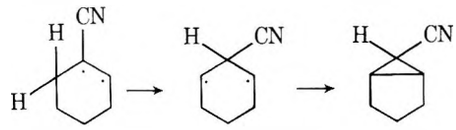
A rationale involving free-radical intermediates can be proposed.



Note that either bond "a" or "b" above could have migrated to the neighboring free-radical center. Either possibility would give the same product in the case of **1**. However, in the case of the tetramethyl nitrile **2**, migration of bond "b" will give a different product, i.e., **9**, from migration of bond "a", i.e., **10**. This question was resolved by a synthesis of the product of migration of bond "a". This product proved to be different from the major photoproduct from **2** and the structure assigned to the major photoproduct therefore seems secure. The second type of product formed in the irradiation is the secondary nitriles, **6** and **8**.



To form these products from the cyclohexenecarbonitrile starting materials, a hydrogen shift must take place. The latter



type of products, although formed in both reactions, was quite unexpected.

Experimental Section

Materials and Instrumentation. Hexane (Baker Analyzed Reagent) was purified by stirring with 30% fuming sulfuric acid, followed by washing with water, sodium carbonate solution, and water, and careful fractional distillation. The purified material had bp 69 °C and a UV absorbance (1-cm path) of 1.0 at 195 nm, 0.05 at 230 nm. Cyclopentene was either from Aldrich (99%) or was prepared by dehydration of cyclopentanol with 88% orthophosphoric acid.[10] Cyclohexene-1-carbonitrile was synthesized by the literature procedure.[2] Dimethyl sulfoxide (Fisher Certified Grade), isophorone (Eastman Practical Grade), and 1-methyl-2-pyrrolidinone (Aldrich) were all distilled prior to use. Cuprous cyanide (Fisher Certified Grade), sodium hydride (Baker, 50% dispersion in oil), and silica gel for column chromatography (Baker Analyzed Reagent, 60–200 mesh) were used as received.

Analytical VPC was performed on a Varian Aerograph Model 204-B dual-column instrument fitted with a flame-ionization detector. The carrier gas was helium and a 5 ft × 1/8 in. stainless steel column packed with 4% QF-1 on 60–80 mesh Chromosorb W was used. Preparative VPC was conducted using a Varian Aerograph Model 200 with a thermal-conductivity detector. The column used was 5 ft × 1/4 in. 7% QF-1 on 60–80 mesh Chromosorb W; the carrier gas was helium. Nuclear magnetic resonance spectra were run using either a Varian FH-390 90-MHz instrument or a Varian HR-220 220-MHz spectrometer. All spectra were run in $CDCl_3$ solvent using tetramethylsilane as internal standard; chemical shifts are given in parts per million downfield from this standard. Infrared spectra were run on a Perkin-Elmer RMU 6A instrument. Elemental microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

All photolyses were run under argon using a Hanovia Type L450 W lamp in conjunction with a water-cooled quartz immersion well.

Photolysis of Cyclohexene-1-carbonitrile (1): Cyclohexene-1-carbonitrile (100 mg, 0.93 mmol) in hexane (400 mL) was thoroughly purged with argon and irradiated for 24 h under argon. After 14 h irradiation, the lamp well was scrubbed clean as a thick deposit tended to coat the walls. After removal of the solvent, VPC analysis (80 °C, helium at 60 mL/min) of the residual yellow oil showed the presence of two components, retention times 4.5 and 6.5 min, in the approximate ratio 1:1. These products were separated by preparative VPC and found to be bicyclo[3.1.0]hexane-1-carbonitrile and *exo*- and

endo-bicyclo[3.1.0]hexane-6-carbonitrile **7** and **6**, as described in the text.

Synthesis of Bicyclo[3.1.0]hexane-6-carbonitrile (6). Diazoacetonitrile was prepared by a modification of the method of Harper and Sleep.[11] Methyleneaminoacetonitrile[12] (18.7 g, 0.275 mol) was stirred with 135 mL of 2 N HCl overnight. The mixture was cooled to −5 °C with acetone–dry ice and 100 mL of methylene chloride was added. To the cooled and stirred mixture was added dropwise an ice-cold solution of sodium nitrite (22.8 g in 70 mL of H_2O); 5% sulfuric acid (25 mL) was then added slowly, the temperature being kept below 0 °C at all times. The mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous layer was extracted with 50 mL of methylene chloride and the combined organic extracts were washed thoroughly with 10% sodium bicarbonate solution. After drying over sodium sulfate, the solution was concentrated to approximately 10 mL by carefully removing the methylene chloride via a 35 × 2.5 cm column of glass helices at aspirator pressure. No external heating was used as the yellow diazoacetonitrile tended to co-distil if the temperature rose to above approximately 25 °C. Purified hexane (50 mL) was added and this mixture was slowly dripped into cyclopentene (6 mL) and copper powder (150 mg) under dry nitrogen. Immediate evolution of nitrogen was observed which subsided after 1 h of stirring. A further 150 mg of copper powder was added and the mixture was refluxed for 1 h, after which time the mixture was filtered and poured into 100 mL of 2 N HCl. The organic layer was separated, washed with 10% sodium bicarbonate, and dried over sodium sulfate. Removal of the solvent yielded 1 g of yellow oil, which on VPC showed the presence of two major products at retention times of 5 and 7 min (80 °C, helium at 60 mL/min) in the approximate ratio 3:2. A small amount of fumaronitrile was also present, which was brominated (1 drop of Br_2), prior to distillation. Fractional distillation yielded 150 mg of a colorless, low-boiling fraction [bp ~35 °C (20 mm)] the NMR and mass spectra of which showed it to be chloroacetonitrile, presumably formed via attack of cyanocarbene on residual methylene chloride.[13] The residue from the distillation was subjected to preparative VPC (90 °C helium at 60 mL/min), the two major peaks, epimers of **6**, were collected together and distilled.

Anal. Calcd for C_7H_9N: C, 78.50; H, 8.41; N, 13.08. Found: C, 78.35; H, 8.39; N, 12.95%.

Synthesis of Bicyclo[3.1.0]hexane-1-carbonitrile (7). A suspension of dimethyloxosulfonium methylide in dimethyl sulfoxide was prepared from sodium hydride (0.504 g, 0.021 mL), trimethyloxosulfonium iodide (4.62 g, 0.021 mol) and Me_2SO (25 mL) by the method of Cory.[6] Cyclopentene-1-carbonitrile (1.86 g, 0.02 mmol) in dimethyl sulfoxide (5 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 2 h and then at 50 °C for 1 h. It was then poured into water (80 mL) and extracted with two 25-mL portions of ether. The ether layer was dried, the ether removed, and the residue distilled to yield 0.35 g (16%) of bicyclo[3.1.0]hexane-1-carbonitrile, bp ~75 °C (12 mm).

Anal. Calcd for C_7H_9N: C, 78.50; H, 8.41; N, 13.08. Found: C, 78.42; H, 8.28; N, 13.22.

Synthesis of 1-Chloro-3,3,5,5-tetramethylcyclohex-1-ene (5). 3,3,5,5-Tetramethylcyclohexanone[14] (12.3 g, 0.08 mol) in methylene chloride (30 mL) was added dropwise to a slurry of phosphorus pentachloride (18.5 g, 0.09 mol) and methylene chloride (60 mL). The mixture was refluxed overnight, cooled, poured onto ice, and extracted with ether. The ethereal extracts were washed with 10% sodium bicarbonate and dried over sodium sulfate. After removal of the ether, the residue was distilled, yielding 7.7 g of 1-chloro-3,3,5,5-tetramethylcyclohexene [bp 75 °C (10 mm)]; yield, 56%.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.58; H, 9.86; Cl, 20.56. Found: C, 69.54; H, 9.92; Cl, 20.43.

Synthesis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile (2). 1-Chloro-3,3,5,5-tetramethylcyclohexene (7.7 g, 0.045 mol) was added to a stirred suspension of cuprous cyanide (7.7 g) in *N*-methyl-2-pyrolidinone (50 mL) and the mixture refluxed for 2 h. The mixture was cooled, poured into 100 mL of 5% sodium cyanide solution, and extracted with two 50-mL portions of benzene. The organic extract was washed with 100 mL of 10% sodium cyanide and 100 mL of water and then dried over sodium sulfate. After removal of the benzene, the residue was distilled to yield 4.5 g (62%) of 3,3,5,5-tetramethylcyclohexene-1-carbonitrile [bp 45–47 °C (0.2 mm)].

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 80.63; H, 10.37; N, 8.29.

Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile (1.5 g, 9.2 mmol) in hexane (3 L) was thoroughly purged with argon and irradiated for 24 h under argon. The hexane was removed under aspirator pressure. VPC analysis (100 °C, helium at 60 mL/min) of the residue showed the presence of two major components in the approximate ratio 4:1, with retention times 6 and 7 min. The major product was isolated by column chromatography on silica gel (55 × 2.5 cm column) using benzene/hexane (1:1) as eluent for the first 800 mL followed by pure benzene; 100-mL fractions were collected and fractions 10, 11, and 12 contained the major product of the photolysis. Distillation of these fractions yielded 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (**9**; 450 mg, 30%), bp 60–62 °C (0.1 mm).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 80.81; H, 10.53; N, 8.48.

The minor component was isolated by preparative VPC (100 °C, helium at 90 mL/min). Its identification as 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile (**8**) is described in the text.

Low Conversion Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. The nitrile (100 mg, 0.6 mmol) in hexane (400 mL) was irradiated for 5 h under argon. Removal of the hexane left a yellow oil, the VPC of which (100 °C, 60 mL/min) showed the presence of three components, two of which coincided with the products formed upon prolonged photolysis. Isolation of the new product was effected by preparative VPC (100 °, 90 mL/Min) and its spectral properties were found to be consistent with the structure 2,2,4,4-tetramethylcyclopentyl-1-acetonitrile. The major product was isolated under the same VPC conditions and its NMR spectrum showed it to be mainly the bicyclic carbonitrile previously characterized. There were, however, two new resonances in the NMR spectrum, a triplet at δ 5.06 ppm (J = 1 Hz) and a doublet at δ 2.56 ppm (J = 1 Hz). It appeared that a compound similar to the new product, which was not separable from the major product by VPC, was present.

Synthesis of 3,3,5,5-Tetramethylcyclopentene-1-carbonitrile (12). 3,3,5,5-Tetramethylcyclopentene-1-carboxamide[7] (4 g, 0.024 mmol) was dissolved in pyridine (5 mL), and tosyl chloride (5 g, 0.026 mmol) was added in small portions. The mixture was stirred for 3 h. Ether (25 mL) was added, the solution was washed with water, and the organic layer was dried over sodium sulfate. After removal of the ether, distillation yielded 2.7 g (60%) of 2,2,4,4-tetramethylcyclopentene-1-carbonitrile, bp 70–72 °C (13 mm).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.54; H, 10.07; N, 9.40. Found: C, 80.34; H, 9.99; N, 9.28.

Synthesis of 2,2,4,4-Tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (10). A suspension of dimethyloxosulfonium methylide in dimethyl sulfoxide was prepared, according to the method of Corey,[6] from sodium hydride (0.013 g, 0.01 mol), trimethyloxosulfonium iodide (1.1 g, 0.005 mol), and Me_2SO (15 mL). 2,2,4,4-Tetramethylcyclopentene-1-carbonitrile (0.7 g, 0.005 mol) in Me_2SO (5 mL) was added slowly with stirring. The mixture was heated to 90 °C and stirred for 3 days, additional portions of dimethyloxosulfonium methylide being added every 24 h. After this time, the mixture was poured into 25 mL of cold water and extracted with two 25-mL portions of ether. The ether extracts were dried and evaporated and distillation of the residue yielded 0.5 g (66%) of 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile, bp 90–92 °C (10 mm).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 81.45; H, 10.16; N, 8.33.

Synthesis of Cyclopentene-1-carbonitrile. Cyclopentanone cyanohydrin (27.8 g, 0.25 mol), from cyclopentanone (21 g, 0.25 mol), was dehydrated with phosphorus oxychloride following the literature procedure.[1] Distillation yielded 10.4 g of colorless liquid, bp 60 °C (9 mm), which was dissolved in 50 mL of dry *tert*-butyl alcohol. Potassium *tert*-butoxide (3.5 g, 0.05 mol) was added and the mixture was refluxed for 1 h after which time it was poured into 100 mL of ice–water. The aqueous mixture was extracted with two 50-mL portions of Et_2O, the organic layer was dried (Na_2SO_4), the ether removed, and the residual oil distilled to yield 8.1 g of cyclopentene-1-carbonitrile, bp 67–70 °C (15 mm).

Anal. Calcd for C_6H_7N: C, 77.18; H, 7.59; N, 14.99. Found: C, 77.42; H, 7.55; N, 15.05%.

Acknowledgment. We thank the National Research Council of Canada for financial support.

Registry No.—**1**, 1855-63-6; **2**, 63261-34-7; **4**, 14376-79-5; **5**, 66323-36-2; *endo*-**6**, 63261-36-9; *exo*-**6**, 63261-35-8; **7**, 31357-72-9; **8**, 63261-38-1; **9**, 63261-37-0; **10**, 66323-37-3; **11**, 66323-38-4; **12**, 66323-39-5; dimethyloxosulfonium methylide, 5367-24-8; cyclopentene-1-carbonitrile, 3047-38-9; diazoacetonitrile, 13138-21-1; cyclopentene, 142-29-0.

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Coordinative Role of Alkali Cations in Organic Synthesis. 3.[1] Selective Methylations of 5-Hydroxy-2-hydroxymethyl-γ-pyrone

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Methylation of 5-hydroxy-2-hydroxymethyl-γ-pyrone (kojic acid, **1**) has been investigated using dimethyl sulfate and caustic alkalis to obtain 5-methoxy (**2**), 2-methoxymethyl (**3**), and 5-methoxy-2-methoxymethyl (**4**) methyl ethers free of each other. The phenolic OH of **1** is methylated through salification, whereas the alcoholic one is methylated due to its coordination with the alkali cations (M^+); the former can be selectively methylated using a stoichiometric amount of an alkali of a low charge density M^+(KOH), the latter by employing excess alkali of a high charge density M^+(LiOH), and both with the alkali of a medium charge density M^+(NaOH). When KOH is the alkali and excess methylating reagents are used, a large amount of the substrate is lost as K^+–**2** complexes in the aqueous phase. Opening of the γ-pyrone ring is attributed to the coordination of its carbonyl with H^+ (in acidic medium) or M^+ (in alkaline medium); in alkaline medium, **1** and **3** do not undergo ring opening due to the creation of an electron-supplying phenoxide.

Methylation of kojic acid (**1**) with dimethyl sulfate (DMS) in aqueous caustic alkalis (MOH) leads[2–4] to all three possible ethers **2**, **3**, and **4**. However, selective preparation of **3** and **4** in high yields was never achieved and it is not convenient to separate them. Coordination of neutral organic nucleophiles with alkali cations (M^+) is becoming known,[5–11] so we attribute their low yields to the formation of water-soluble complexes with M^+; we indeed isolated a number of alkali sulfate complexes of **2** from the aqueous phase of reaction mixtures involving use of excess DMS and KOH.[12] This paper reports the results of a detailed systematic study leading to procedures by which each of the three ethers can be obtained free of the other in 60 to 75% yields.

The reactants of a reaction mixture are written in the order **1**, DMS, MOH such that the reaction mixture 142 denotes 1–DMS–MOH (1:4:2). Experimental conditions of a reaction are also described by notations; 132 (KOH), 10 aq, DMS (↓), 25 °C reads that 1–DMS–KOH (1:3:2) was the reaction mixture in 10 mL of water where DMS was added to the 1–KOH system maintained at 25 °C.

Results and Discussion

The results of selected experiments are shown in Table I and synthetic routes in Scheme I. Employing 111 reactions, only phenolic OH was methylated to obtain **2** (Scheme I, reaction a). Methylation, however, was hampered and M^+–OkH (metal kojate) instead of **2** was mainly recovered for LiOH and

Scheme I. Routes of Methylation Reactions of Kojic Acid

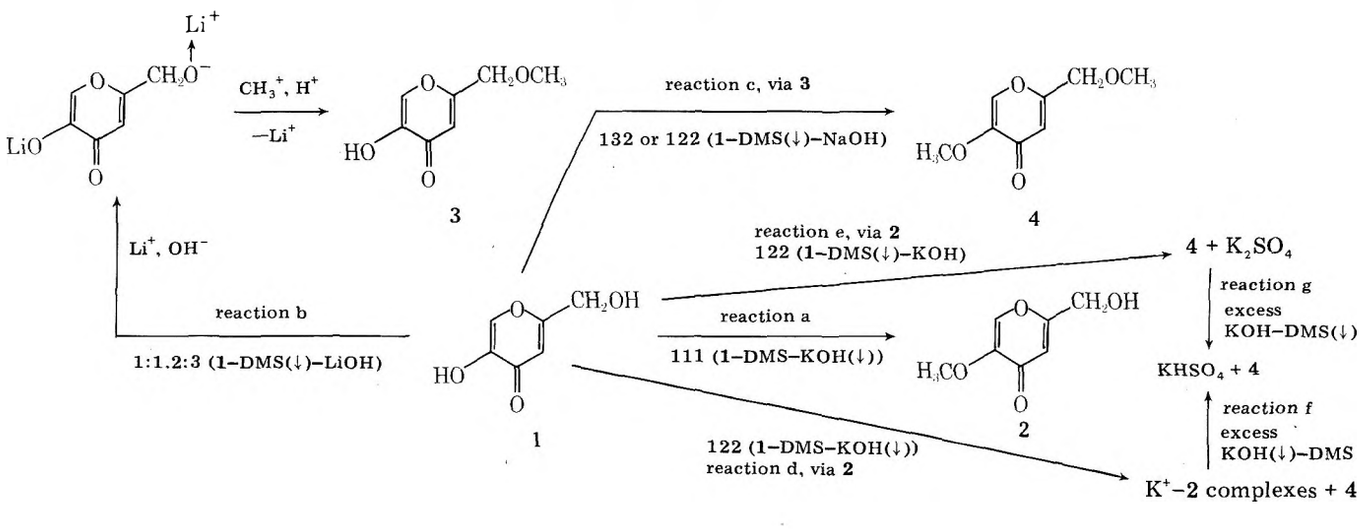

Table I. Results of Selected Methylation Experiments

Reaction conditions	Recovery Procedure	Methylation product (s) (% yield)	Remarks
111 (NaOH), 10 aq, NaOH (↓), 20–5 °C	cy	**2** (75)	Recommended for prep. of **2**
111 (NaOH), 10 aq, DMS (↓), 40–45 °C	cy (**2**), ex (**4**)	**2** (62) + **4** (5)	*a*
111 (KOH), 10 aq, KOH (↓), 20–25 °C	cy	**2** (74–76)	Recommended for prep. of **2**[b]
123 (LiOH), 10 aq, DMS (↓), 20–25 °C	ex	**3** + **4**	Low yields[c,d]
113 (LiOH), 10 aq, DMS (↓), 20–25 °C	ex	**3** + some **4**	Low yields[e]
1:1.2:3 (LiOH), 10 aq, DMS (↓), 40–45 °C	ex	**3** (60)	Recommended for prep of **3**; see ref 13
122 (NaOH), 10 aq, NaOH (↓), 20–25 °C	cy(**2**) + ex (**4**)	**2** (18) + **4** (12)	*e*
122 (NaOH), 10 aq, DMS (↓), 40–45 °C	ex	**4** (48)	
132 (NaOH), 25 aq, DMS (↓), 40–45 °C	ex	**4** (58–60)	Recommended for prep of **4**[f]
144 (NaOH), 10 aq, DMS (↓), 40–45 °C	ex	**4** (46) + some **3**	*g, h*
144 (KOH), 10 aq, DMS (↓), 25–30 °C	cy ($KHSO_4$), ex (**4**)	$KHSO_4$ + **4** (22)	*h*

[a] High temperature of the reaction favors methylation of $-CH_2OH$ (even in 111 reaction mixture). [b] Contrary to expectations, yield of **2** using KOH is not better than the one with NaOH which is understandable because some **2** is lost as K^+–**2** complexes. [c] Yields are low because excess alkali hampers methylation of phenolic OH and reaction temperature is not high enough to favor methylation of $-CH_2OH$. [d] Not possible to know the respective yields of **3** and **4**. A rough assessment is possible because the **3**–**4** oil affords partial crystallization of **4** in about a week. [e] Methylation of $-CH_2OH$ is not favored because reaction temperature is low and the entire alkali has not been taken right from the start of the reaction. [f] The yield of **4** is boosted by using a dilute reaction mixture because methylation of the phenolic OH is favored due to loosening of the $Na^+{}^-OkH$ ion pair and that of $-CH_2OH$ due to a decreased association of $Na_2{}^+SO_4{}^{2-}$ and hence availability of Na^+ for $-CH_2OH \rightarrow Na^+$ coordination. [g] Although NaOH and DMS are stoichiometric and are used in excess, methylation of phenolic OH is not efficient. This is because (i) the reaction starts with a high NaOH/1 ratio and (ii) due to high temperature of the reaction excess NaOH destroys a substantial amount of DMS. [h] Too much of MOH and DMS is unfavorable to the yield of **4** due to mutual destruction of MOH and DMS and destructive reactions of **4**.

when in the use of NaOH the reaction mixture was processed below 20 °C or contained nonaqueous solvent (methanol).

Employing excess MOH and DMS, the main product was **4**. When the amount of MOH outweighed that of DMS, especially in the case of NaOH and LiOH (reactions b and c), the phenoxide of **1** was protected by M^+ against incipient $CH_3{}^+$ and **4** was produced contaminated with **3**. This observation ultimately led us to discover a procedure for the selective methylation of alcoholic groups[13] to obtain **3** and explains why **3** was obtained[2] from the 1–DMS–KOH (1:3.7:6) reaction mixture which involves the use of excess methylating agents.

When the amount of DMS exceeded that of MOH, **4** was obtained at the expense of **3** because due to the availability of $SO_4{}^{2-}$ ions from DMS the equilibrium

$$2M^+{}^-OkMe + SO_4{}^{2-} \rightleftharpoons {}^-OkMe + M_2SO_4$$

is shifted to the right and unprotected phenoxide of ^-OkMe was methylated (reaction c). This explains how **4** uncontaminated with **3** could be obtained from 198 1–DMS–KOH[4] inspite of KOH being used in eightfold excess. When methylating agents are in excess and MOH is KOH, production of **4** and **3** still depends on the DMS/KOH ratio but K^+–**2** complexes are also produced due to which yield of the ethers is lowered. The side reaction is pronounced especially when KOH is added to 1–DMS (reaction d), for production of **2** as an intermediate is favored which functions as a ligand for K^+ and diverts the reaction to produce K^+–**2** complexes. If only KOH is present along with **1** from the start (reaction e), methylation of $-CH_2OH$ of the intermediate is promoted and so is the yield of **4** at the expense of complexes.

The 144 or 166 1–DMS–KOH reactions produce **4** plus $KHSO_4$ irrespective of the sequence in which KOH and DMS are used (reactions f and g). Obviously, the K^+–**2** complexes produced via reaction d are ultimately methylated and due to the weak ligating power of the organic counterpart in the methylation product are decomposed to yield **4** and $KHSO_4$.

Recovery and Yield of Methyl Ethers. The yield of **2** (~75%) employing the recommended procedure is comparable to the reported one (72%) with the same method[3] but less comparable to the diazomethane method;[14,15] the latter method is, however, inconvenient and, due to the insolubility of **1** in the nonpolar medium of synthesis, is applicable to a few grams of the sample at a time.

The recovery of **3** and **4** employing benzene extractions is inefficient due to their high hydrophilicity and due to extraction being pH dependent. Their yield and quality become poor as solution pH falls below 2 and extraction temperature exceeds 50 °C. Extraction is not possible from alkaline solutions where ethers exist as anions: **3** due to salification of the phenolic OH and **4** due to ring opening followed by salification of the enole. Extraction takes place best at a pH which ensures maximum stability of the γ-pyrone ring and in the case of **3** prevents ionization of the molecule; pH 7 for **4** and 5.5–6 for **3**.

Mechanism of Methylation. Methylation of the phenolic OH is favored when MOH is added slowly to 1–DMS and methylation of the alcoholic OH is favored when MOH is taken along with **1** from the start of the reaction. This indicates that (i) for methylation of the phenolic OH the MOH/DMS ratio should be minimum at every stage of the reaction so that ionization of the $M^+{}^-OkH$ pair and hence $M^+/CH_3{}^+$ exchange is favored and (ii) for methylation of the alcoholic OH the MOH/DMS ratio should be high throughout the reaction so that "activation" of this group through the formation of

$$\begin{array}{c} -CH_2OH^+ \\ \downarrow \\ M^+ \\ \mathrm{I} \end{array}$$

and hence elimination of the polarized proton is facilitated.

The validity of I coordination during methylation of $-CH_2OH$ appears justified because (i) the M^+–**2** complexes are actually isolated which do not show the infrared and ^1H NMR characteristics of the ligand[12] and (ii) x-ray analysis has revealed coordination of the $-CH_2OH$ group with M^+ in $KI(PkH)_2$[8] and $CsNCS(PkH)$[16] where PkH is phenacylkojate.

On Opening of the γ-Pyrone Ring. It is known that γ-pyrone ring normally opens in an alkaline medium.[17] We note that the same is "damaged" even in an acidic solution. This suggests that the Lewis acid part of the inorganic species (H^+ or M^+) gets coordinated to the carbonyl of the ring and aids its electron depletion. Due to stabilization of the Lewis acid with the ring, the base counterpart becomes available in a comparatively destabilized state for the nucleophilic attack on the pyrone oxygen; coordination of the carbonyl of the kojate moiety of phenacylkojate has been revealed (by x-ray analysis) for the water proton in PkH, H_2O[18] and for M^+ in $KI(PkH)_2$[8] and $CsNCS(PkH)$[16] whereas electrostatic destabilization and hence an enhanced nucleophilicity of X^- after complexation of the counter M^+ has been demonstrated during the coordination studies of the alkali salts, MX.[7,19,20]

Experimental Section

General Procedure for Methylation. To a solution of **1** (1.77 g, 12.5 mmol) in the concerned medium (10 mL) was either added the desired amount of DMS and the solution was titrated with the desired amount of 50% aqueous MOH or a weighed amount of MOH was added and the solution was slowly treated with DMS. In either case the titrant was added slowly in about 30 min while the reaction mixture was shaken and the latter was then allowed to rest for another 30 min before subjecting it to the recovery of the products.

Recovery of Methylation Products. (i) From Stoichiometric Reaction Mixtures. NaOH (at 20–25 °C) and KOH (20 °C) reaction mixtures produced only **2** which was crystallized by cooling and collected by filtration. After removal of the first crop (c_1), the filtrate was concentrated to 3–4 mL and the second crop (c_2) was collected similarly—procedure cy. LiOH reaction mixtures and those of NaOH processed below 20 °C produced metal kojates, $M^+{}^-OkH$, as c_1 so that **2** was recovered from the filtrate as c_2.

(ii) From Reaction Mixtures Employing Excess Methylating Reagents. A mixture of LiOH or NaOH (which produces **4** or **4** plus **3**) was adjusted at pH 6–7 employing 2 N H_2SO_4 or NaOH and was evaporated to a slurry employing a rotary evaporator. The methyl ether was extracted employing seven 20-mL lots of benzene (the best extractant we found) at 70–80 °C. About 120 mL of the collected extracts was recovered by distillation and recovery of the ether(s) was attempted from the concentrate after its dehydration (with molecular sieve 4 Å pores), decolorization (with activated charcoal), and evaporation to dryness at room temperature—procedure ex. Crystals (mp 85–88 °C) were obtained in case the product was pure **4** but only oil was obtained when the latter was contaminated with **3**.

A mixture of KOH, in addition to **4** (or **4** + **3**), produced also one or more complexes of K^+. Either the ether(s) was removed first employing procedure ex and then the complex(es) was removed employing procedure cy (procedure ex–cy) or first the complex was removed and then the ether—procedure cy–ex.

Characterization of Methyl Ethers. **1** (mp 154 °C; 8.38, 6.83, 4.80 ppm), **2** (mp 165 °C; 8.35, 6.82, 4.80, 4.07 ppm), **3** (mp 75 °C; 7.88, 6.38, 4.55, 4.26, 3.32 ppm), and **4** (mp 90 °C; 7.80, 6.35, 4.50, 4.78, 3.65, 3.33 ppm) were characterized employing (i) 80 MHz ^1H NMR in Me_2SO-d_6, (ii) $FeCl_3$ test which is responsive in neutral medium by **1** and **3**, and (iii) by comparing their melting points with those reported in the literature.[2–4,14,15]

Recommended Procedures for Preparation of Methyl Ethers. (i) Synthesis of 2 by taking **1** (1.77 g), DMS (1.57 g), and KOH (0.7 g) and employing a 111 (KOH), 10 aq, KOH (↓), 20 °C reaction. After addition of KOH is complete, crops c_1, c_2, and c_3 were collected employing procedure cy. The yield of the yellowish crude product is ~1.48 g (75–76%; mp 158–62 °C). The product was recrystallized after decolorization with activated charcoal from ethanol. The colorless crystals melted at 164–65 °C.

(ii) Synthesis of 3 by taking **1** (1.77 g), DMS (1.89 g), and LiOH, aq (1.57 g), and employing a 1:1.2:3 (LiOH), 10 aq, DMS (↓), 40–45 °C reaction. After addition of DMS was complete and the reaction solution had been allowed to rest for another 30 min, the pH was adjusted at 5.5–6 with 2 N H_2SO_4 and the ether was recovered employing procedure ex. The yield of the brownish crystals was ~1.25 g (60%; mp 70–2 °C). Recrystallization, after decolorization with activated charcoal, from benzene yielded colorless crystals melting at 74–5 °C.

No effort was made to make the conditions drastic to promote methylation of the alcoholic group for this cannot be done without simultaneous methylation of the phenolic OH.[13]

(iii) Synthesis of 4 by taking **1** (1.77 g), DMS (4.72 g), and NaOH (1.0 g) and employing a 132 (NaOH), 20 aq, DMS (↓), 40–45 °C reaction. After addition of DMS was complete and the reaction solution had been allowed to rest for another 30 min, the pH was adjusted at 7 using 1 N NaOH. **4** was extracted employing procedure ex. The yield was ~1.27 g (60%; mp 88 °C). The product was recrystallized after decolorization with activated charcoal from benzene to obtain colorless crystals melting at 90 °C.

No effort was made to favor methylation of the two hydroxy groups by raising the reaction temperature beyond 45 °C for this leads to the mutual destruction of NaOH and DMS as well as that of **4** with NaOH.

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Registry No.—**1**, 501-30-4; **2**, 6269-25-6; **3**, 54620-68-7; **4**, 54620-66-5.

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A New Synthetic Route to *tert*-Butyloxycarbonylaminoacyl-4-(oxymethyl)phenylacetamidomethyl-resin, an Improved Support for Solid-Phase Peptide Synthesis[1]

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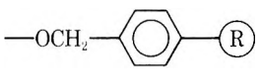
The preferred route to the aminoacylated 4-(oxymethyl)phenylacetamidomethyl-resin (-OCH_2-Pam-resin) involves the condensation of a Boc-aminoacyl-4-(oxymethyl)phenylacetic acid (Boc = *tert*-butyloxycarbonyl) with aminomethyl-resin. Aminomethyl-resin was synthesized by direct amidoalkylation of polystyrene resin to give the phthalimidomethyl-resin. The extent of reaction was monitored by IR, allowing the reaction to be stopped at any chosen level of substitution. Hydrazinolysis gave aminomethyl-resin. The Boc-amino acid was converted in solution to a substituted benzyl ester by reaction with 4-(bromomethyl)phenylacetic acid phenacyl ester. Zinc–acetic acid reduction removed the phenacyl group to give the Boc-aminoacyl-4-(oxymethyl)phenylacetic acid, which was coupled to aminomethyl-resin with DCC. The benzyl ester bond of the resulting aminoacyl-OCH_2-Pam-resins was approximately 100-fold more stable in refluxing trifluoroacetic acid than the aminoacyl-OCH_2-resin. Comparison with a solution analogue showed that this was due to the inductive effect of the *p*-acetamidomethyl group. Cleavage yields (HF–anisole, 9:1 v/v, 30 min, 0 °C) were 82–100% for the aminoacyl- and peptidyl-OCH_2-Pam-resins examined. The aminoacyl-OCH_2-Pam-resins showed resistance to primary amine nucleophiles similar to that of the aminoacyl-OCH_2-resin. No racemization (<0.1%) occurred in the synthesis of Boc-L-Val-OCH_2-Pam-resin, and this resin gave improved results in syntheses of the model peptides Leu-Ala-Gly-Val and ribonuclease A (111–124).

It is known that some of the peptide chains covalently bound to oxymethylpoly(styrene-*co*-divinylbenzene) resin (**1**), the support commonly used for solid-phase peptide synthesis,[3,4] are lost by acidolysis during the synthesis.[5–8] The resin 4-(oxymethyl)phenylacetamidomethylpoly(styrene-*co*-divinylbenzene) (**2**) was introduced to minimize this loss.



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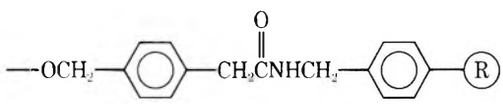

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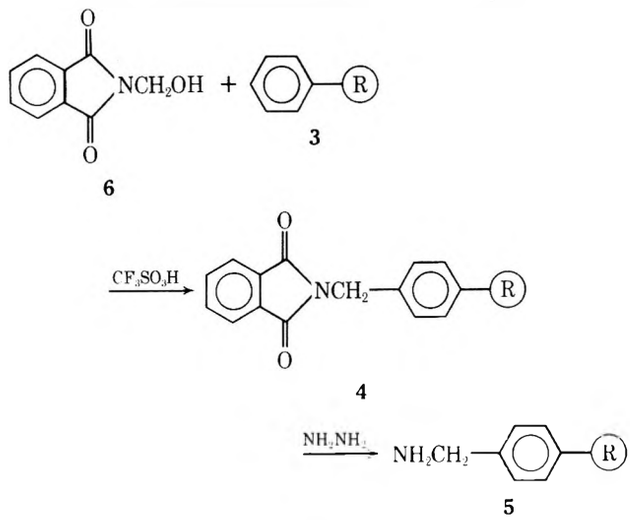
The presence of the electron-withdrawing phenylacetamidomethyl (Pam) bridge was shown to increase the stability of the peptide ester of **2** by 100-fold relative to the peptide ester of **1**, in 50% trifluoroacetic acid in dichloromethane.[9] Use of Pam-resin is expected to result in much higher yields of large peptides prepared by solid-phase peptide synthesis. It is also important that the aminoacyl-OCH_2-Pam-resin can be prepared by routes which avoid side reactions known to be possible in the preparation of aminoacyl-OCH_2-resin from chloromethyl-resin, and that this chemically well-defined resin exhibits improved results in peptide synthesis.

In this article we report our exploration of synthetic routes to aminoacyl-OCH_2-Pam-resins. We have devised a convenient general synthesis of Boc-aminoacyl-4-(oxymethyl)-phenylacetic acids, the key intermediates in the preparation of the aminoacyl-OCH_2-Pam-resins from aminomethyl-resin. Aminomethyl-resin has been prepared on a large scale directly from polystyrene resin without the intermediacy of chloromethyl-resin. In addition, further data are presented on the low trifluoroacetic acid labilities of several Boc-aminoacyl-OCH_2-Pam-resins, their high HF cleavage yields, and their resistance to amine nucleophiles.

Results and Discussion

A. Aminomethyl-resin (5). Aminomethyl-resin (**5**) previously used in the preparation of Pam-resin was synthesized via the chloromethyl-resin.[9–12] A preparation of **5** from unsubstituted polystyrene by direct amidoalkylation (the Tscherniac–Einhorn reaction[13]) was recently developed in this laboratory[14] (Scheme I). This avoids the use of the carcinogenic reagent chloromethyl methyl ether.[15] In addition, Scheme I requires one less step, the reactions are easy to perform, and the undesirable side reactions of the chloromethyl-resin are not possible.[4]

Scheme I. Preferred Route to Aminomethyl-resin



6 **3** **4** **5**

The preferred reagent for this synthesis is the readily available *N*-(hydroxymethyl)phthalimide (**6**), with trifluoromethanesulfonic acid as catalyst. Polystyrene–divinylbenzene copolymer beads were thoroughly washed before use to remove residual monomer, crosslinking agent, catalyst, and additives remaining from the polymerization, and noncrosslinked oligomer. The amidoalkylation proceeds smoothly in 50% (v/v) trifluoroacetic acid–dichloromethane as solvent at room temperature, and the extent of reaction can be readily controlled by IR monitoring of resin samples. The ratio of the intensity of the phthalimide carbonyl band at 1720 cm^{-1} to that of the polystyrene at 1601 cm^{-1} allows the degree of substitution to be approximately determined, and the reaction can be terminated at the desired level by filtration and washing. For the levels of substitution required for use in solid-phase peptide synthesis (≤1 mmol/g), the reaction rapidly (<6 h) proceeds to completion if only the calculated

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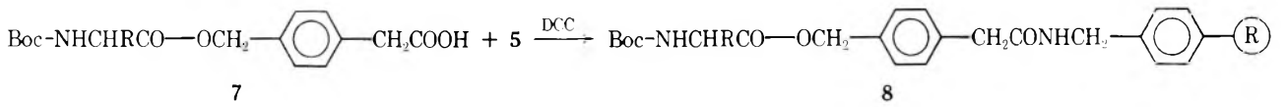
Scheme II. Preferred Route to Boc-aminoacyl-OCH_2-Pam-resin



7 8

amount of *N*-(hydroxymethyl)phthalimide is used. This is the simplest method of precisely obtaining a predetermined loading. In addition, we have varied the concentrations of reagent and catalyst and the reaction time to yield phthalimidomethyl-resin (**4**) having substitutions of 0.05–3.60 mmol/g. Hydrazinolysis in refluxing ethanol gives the aminomethyl-resin (**5**). Both of these steps have been conveniently carried out on 10-mg to 200-g amounts of resin.

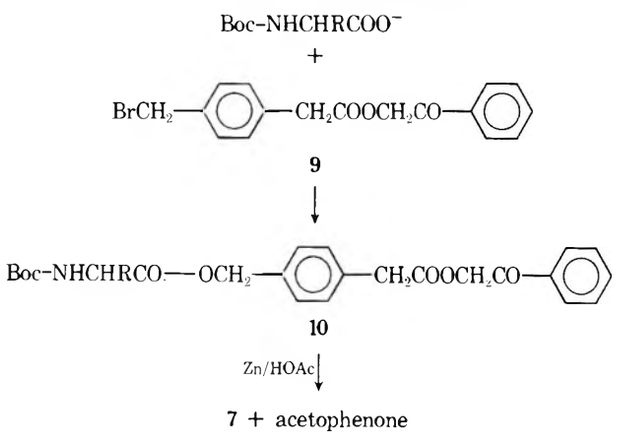
B. Synthesis of Boc-aminoacyl-4-(oxymethyl)-Pam-resin (8). There are two approaches to Boc-aminoacyl-OCH_2-Pam-resins. In the first of these, the Boc-amino acid is derivatized to form the Boc-aminoacyl-4-(oxymethyl)-phenylacetic acid which, after purification, is coupled to the aminomethyl-resin. This is the preferred route. In the second approach the aminomethyl-resin is derivatized with a substituted tolylacetic acid to give a functionalized Pam-resin onto which the C-terminal Boc-amino acid is then loaded. This approach is simpler, but is susceptible to all the side reactions known for the loading of normal resins.

1. First Approach. The most definitive route to a Boc-aminoacyl-OCH_2-Pam-resin (**8**) is illustrated in Scheme II. This approach allows the simultaneous attachment of the C-terminal Boc-amino acid and its benzyl ester protecting group[9] onto the polystyrene support. The acetamidomethyl group that is formed serves both as the covalent link between the benzyl ester and the resin and as the electron-withdrawing substituent that increases the acid stability of the peptide benzyl ester.

The compound **7** containing the amino acid benzyl ester linkage is formed in solution, purified, and characterized. It can then be used to acylate the resin **5** quantitatively under the same mild coupling conditions used in peptide bond formation. The reaction is applicable to all the protected amino acids normally used in peptide synthesis and is generally free from side reactions. This coupling can be readily incorporated into automated syntheses, allowing peptides to be made starting directly from the aminomethyl-resin support. Such a mild unambiguous loading method is a major advantage associated with the use of this route to aminoacyl-OCH_2-Pam-resins (**8**).

a. Preparation of Boc-aminoacyl-4-(oxymethyl)-phenylacetic Acids. A general route to the Boc-aminoacyl-4-(oxymethyl)phenylacetic acids (**7**) would involve the condensation of a Boc-amino acid salt with a carboxyl-protected halomethylphenylacetic acid. The carboxyl protecting group would have to be stable to the conditions of formation of the benzyl ester bond, and selectively removable without affecting the N^{α}-Boc group, the benzyl ester, and any side-chain protecting group present in the amino acid. One carboxyl-protecting group that satisfies the above requirements is the phenacyl ester.[16–18] The successful general route based on the use of this group is shown in Scheme III. The protected compound **9** is readily obtained from the reaction of a salt of 4-(bromomethyl)phenylacetic acid with bromoacetophenone. The use of 4-(bromomethyl)phenylacetic acid[12,19] is preferred over the 4-(chloromethyl)phenylacetic acid because the latter compound is obtained in low yield by the published procedure[20] and is less reactive. Reaction of **9** with a Boc-amino acid salt gives the phenacyl ester (**10**) of the desired product. Removal of excess Boc-amino acid by basic washes gives a product suitable for use without further purification. The phenacyl group can be removed by zinc/acetic acid reduction at room temperature, without cleaving the Boc or benzyl ester groups, to give the desired product **7**. The reduction is readily monitored by proton NMR, which shows clean, rapid cleavage of the phenacyl ester. Provided the starting protected halomethylphenylacetic acid phenacyl ester (**9**) is pure, the final product is free of polycondensation products. Complete removal of excess Boc-amino acid from **10** ensures a final product free of the Boc-amino acid. Workup is by a simple extractive procedure, and residual acetic acid is removed by azeotroping with benzene. The Boc-amino-acyl-4-(oxymethyl)phenylacetic acid (**7**) is obtained from ether as the solid CHA or DCHA salt in good overall yield.

Scheme III. A General Route to Boc-aminoacyl-4-(oxymethyl)phenylacetic Acids



The route shown in Scheme III can be used for a variety of protected amino acids. Most of the commonly used protecting groups are stable to the reductive cleavage conditions.[21] We have prepared the 4-(oxymethyl)phenylacetic acid derivatives of the following amino acids, as CHA salts: Boc-L-Val, Boc-L-Lys(Z), Boc-L-Asp(OBzl), Boc-L-Ser(Bzl), and Boc-L-Met.

A simpler but less general route to **7** is the reaction of the Boc-amino acid salt with a 4-halomethylphenylacetic acid. However, this reaction can give rise to a multiplicity of products in addition to the desired product and unreacted starting material. For example, the halomethylphenylacetic acid can first dimerize before reacting with the Boc-amino acid salt. Further reaction of the desired product with halomethylphenylacetic acid would also give a similar spectrum of products. Although it could be achieved, the purification of the product **7** has been difficult.[9] Preparative thick-layer chromatography was necessary and, in addition to the desired product, the dimeric Boc-aminoacyl-[4′-(oxymethyl)phenylacetyl]-4-(oxymethyl)phenylacetic acid was isolated. Different Boc-amino acids required the development of new solvent systems.

We also explored the use of 4-(bromomethyl)phenylacetic acid *N*-hydroxysuccinimide ester. It was hoped that the *N*-hydroxysuccinimide ester would serve as a carboxyl protecting group during the formation of the benzyl ester bond, and then serve as an active ester to allow the acylation of aminomethyl-resin to give Boc-aminoacyl-OCH_2-Pam-resin (**8**). Unfortunately, the reaction of Boc-valine cesium salt[22] with 4-(bromomethyl)phenylacetic acid *N*-hydroxysuccinimide ester proceeded poorly as determined by thin-layer chromatography of the crude reaction mixture vs. a reference sample of the desired Boc-Val-4-(oxymethyl)phenylacetic acid *N*-hydroxysuccinimide ester. This was presumably due to the

reaction of the carboxylate group with the active ester.[23]

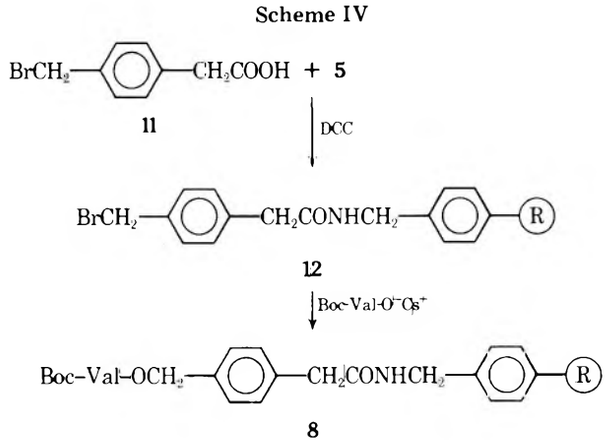
b. Physical Properties, Optical Purity, and Use in Synthesis. This first approach using the Boc-aminoacyl-4-(oxymethyl)phenylacetic acid (7) formed in solution to couple to the aminomethyl-resin (5), as shown in Scheme II, is the route of choice to aminoacyl-OCH_2-Pam-resins (8). Examination of the colorless loaded resin under the microscope showed unpitted translucent spheres identical with the unsubstituted resin, washed or unwashed. There was no evidence of broken or damaged beads. Measurement of the diameters of the aminomethyl-resin and the loaded Pam-resins showed that each swelled in methylene chloride to the same extent (4.4-fold), comparable to the unsubstituted resin (fivefold).[7] Sometimes the resin 8 showed an increased tendency to clump during some manipulations in the course of a synthesis. This had no effect on the excellent synthetic results obtained with the resin. In one instance[24] no clumping was observed in a prolonged stepwise synthesis using a silanized reaction vessel.[25] The loaded resins are optically pure and give good synthetic results, as shown by the following data.

Boc-L-Val-4-(oxymethyl)phenylacetic acid was purified and reacted with aminomethyl-resin (5) to give Boc-L-Val-OCH_2-Pam-resin. This was deprotected and coupled with Boc-L-Leu. The Boc-L-Leu-L-Val-OCH_2-Pam-resin was cleaved and the unpurified dipeptide was subjected to ion-exchange chromatography under conditions that allow the separation and quantitative determination of one part of L-Leu-D-Val in the presence of 1000 parts of L-Leu-L-Val.[26] The absence of L-Leu-D-Val (<0.1%) indicated that the synthesis of Boc-valyl-4-(oxymethyl)phenylacetic acid and its subsequent coupling to aminomethyl-resin proceeded without detectable racemization.

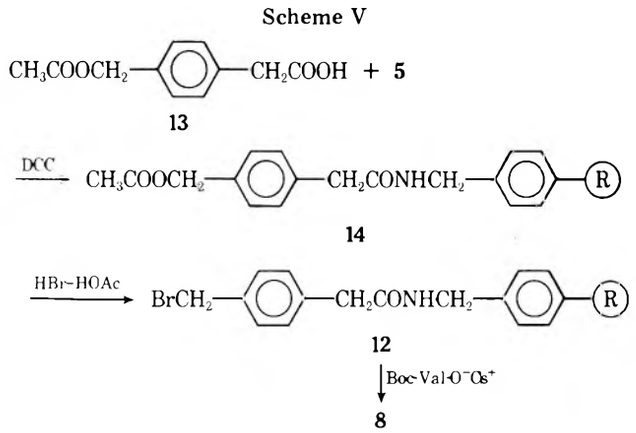
The Boc-Val-OCH_2-Pam-resin described above has been carried through three cycles of synthesis by standard procedures to give Boc-Leu-Ala-Gly-Val-OCH_2-Pam-resin. Treatment of this material with anhydrous HF has resulted in essentially quantitative cleavages, as indicated by recoveries of product peptide and by the levels of amino acids in acid hydrolyzates of the residual resin. Ion-exchange chromatography has routinely indicated the presence of over 99 mol % Leu-Ala-Gly-Val in the unpurified product. Levels of deletion peptides and other byproducts are substantially lower than in identical syntheses performed on normal Boc-Val-OCH_2-resin.

Ribonuclease A (111–124) was also synthesized on Boc-Val-OCH_2-Pam-resin prepared according to Scheme II. A standard double-coupling synthesis, as described for the synthesis of Leu-Ala-Gly-Val, gave the protected tetradecapeptide-OCH_2-Pam-resin. After treatment with HF–anisole (9:1, v/v) for 1 h at 0 °C, the unpurified product was chromatographed on Aminex 50W-X4 in a pyridine–acetate gradient

Scheme IV



Scheme V



as previously described.[27] Chromatography at very high loading showed the desired tetradecapeptide as 94.8 mol % of the ninhydrin-positive products. None of the byproducts was present in more than 1.2 mol%. The peptide contained tritium label in Ala^{122}. Tritium monitoring of the column effluent showed the desired tetradecapeptide, but did not detect further byproducts. Previous syntheses on Boc-Val-OCH_2-resin have given higher levels of byproducts.[27]

2. Second Approach. An example of the preparation of Boc-aminoacyl-OCH_2-Pam-resins (8) by derivatization of aminomethyl-resin (5) prior to the loading of the first Boc-amino acid is shown in Scheme IV. This route to 8 is less desirable, since precise analytical control of the chemistry performed on the functionalized resin **12** is not possible. A similar approach was investigated by Sparrow.[12] The reaction of **5** with DCC-activated **11** should give rise primarily to **12,** but the N-benzylation of some aminomethyl sites by **11** has not been ruled out as a competing side reaction. We have found that Boc-Val-OCH_2-Pam-resin (8) obtained via Scheme IV furnishes the model Leu-Ala-Gly-Val[3,28] containing higher levels of deletion peptides than normally observed in our syntheses from 8 obtained via Scheme II.

An alternative example of this second route which we have investigated is shown in Scheme V. Boc-Val-OCH_2-Pam-resin (8) prepared in this manner allowed the synthesis of Leu-Ala-Gly-Val in high purity.

This sequence avoids the possibility of the N-benzylation side reaction. However, both Schemes IV and V have the drawback that unreacted bromomethyl-Pam sites (**12**) may participate in undesirable side reactions later in a synthesis.[29]

C. Properties of Aminoacyl-4-(oxymethyl)-Pam-resins (8). 1. Acid Stability. The stability of three Boc-aminoacyl-OCH_2-Pam-resins to acidolytic conditions was determined. Boc-Gly-, Boc-Phe-, and Boc-Val-OCH_2-Pam-resins, Boc-Val-OCH_2-resin, and Boc-valyl-4-(oxymethyl)phenylacetamidomethylbenzene (**15**) were refluxed in anhydrous trifluoroacetic acid. The rate constants and the relative rates of cleavage (compared to Boc-Val-OCH_2-resin) of the various benzylic derivatives are given in Table I.

The aminoacyl-OCH_2-Pam-resins are 100- to 200-fold more stable than Boc-Val-OCH_2-resin in refluxing trifluoroacetic acid. The cleavage of Boc-Val-OCH_2-Pam-resin and **15** affords an interesting comparison. The latter soluble derivative was cleaved about fourfold faster than the resin bound analogue. This observation is consistent with the general observation that a reaction within a solid support proceeds somewhat slower than the same reaction in solution.[4] Therefore, it can be concluded that the increased acid stability of the acyl-OCH_2-Pam-resin is not due primarily to steric factors such as the polystyrene backbone, but to the acetamidomethyl group acting as an electron-withdrawing substituent.

The increased stability of acyl-OCH_2-Pam-resins in hot

Table I. Cleavage of Amino Acid Benzyl Ester Derivatives in Refluxing Trifluoroacetic Acid

Benzylic derivative	k_t,[a] 10^{-6} s^{-1}	% loss per min	k_{rel}
Boc-Val-OCH_2-resin	717	4.2	[100]
Boc-Gly-OCH_2-Pam-resin	7.4	0.044	1.0
Boc-Val-OCH_2-Pam-resin	5.1	0.031	0.7
Boc-Phe-OCH_2-Pam-resin	3.6	0.022	0.5
Boc-Val-OCH_2-Pam-benzene	20.4	0.12	2.8

[a] Apparent first-order rate constants were determined from plots of ln $[a/(a - x)]$ vs. time where a is the amino acid content of the starting material and x is the amount of acid released at a given time.

trifluoroacetic acid indicates a possible application of these supports in solid-phase peptide sequencing of resin-bound synthetic peptides.[30] The new preparation of aminomethyl-resin[14] may also be useful for sequencing of free peptides.

2. Cleavage Yields. It is important to note that the lability of the acyl-OCH_2-Pam-resin to anhydrous HF, a cleavage reagent commonly used in solid-phase peptide synthesis, is still adequate despite the increased stability of the acyl-OCH_2-Pam resin to trifluoroacetic acid. Thus, treatment of Leu-Ala-Gly-Val-OCH_2-Pam-resin and the aminoacyl-OCH_2-Pam-resins listed in Table I with 9:1 (v/v) HF–anisole for 30 min at 0 °C resulted in cleavages ranging from 82 (Boc-Phe-OCH_2-Pam-resin) to 100% (Boc-Gly-OCH_2-Pam-resin) as determined by the amount of product released and amino acid analysis of the cleaved resins. It is known that peptides with C-terminal phenylalanine are especially difficult to cleave with HF, and that those with C-terminal glycine are the most readily cleaved.[31] Even with the mild cleavage conditions tested here, phenylalanyl-OCH_2-Pam-resin gave a high cleavage yield.

3. Susceptibility to Amine Nucleophiles. The lability of the benzyl ester bond in acyl-OCH_2-Pam-resins toward attack by primary amines was compared with the lability of the standard acyl-OCH_2-resin under the same conditions (Table II). Runs 1 and 2 indicate that *n*-butylamine penetrates the polystyrene beads and converts all of the chloromethyl sites to butylaminomethyl sites at room temperature (18 h). Runs 3 and 4 show that Boc-aminoacyl-OCH_2-resin and Boc-aminoacyl-OCH_2-Pam-resin have significant lability in neat *n*-butylamine. As expected, reaction of these resins with 5–10% (v/v) amine in methylene chloride proceeded much less rapidly (runs 5–8). Both resins were cleaved at approximately the same rate.

These results show that the aminoacyl-OCH_2-Pam-resins are not significantly more susceptible to nucleophilic attack by primary amines than the aminoacyl-OCH_2-resin. Use of the aminoacyl-OCH_2-Pam-resin in prolonged stepwise synthesis has not resulted in any detectable loss of chains from the resin.[24] In the light of these data, it is not anticipated that the formation of diketopiperazines and concomitant loss of chains observed with the standard aminoacyl-OCH_2-resin will be any greater with the Pam-resin. Methods exist for overcoming this problem where it is observed.[4]

D. Other Applications. The aminomethyl derivative of the non-crosslinked KelF-g-styrene[2] resin[32] has been prepared and converted to Boc-aminoacyl-OCH_2-Pam-(KelF-g-styrene) according to Schemes I and II. A preliminary evaluation[24] of this resin showed properties comparable to those reported for the resin 8.

The chemistry of the Pam-resins that has been discussed in this paper and elsewhere[9] should find ready application in systems not utilizing polystyrene supports. For example, the soluble polyethylene glycol used in the liquid-phase method of peptide synthesis[33,34] could be modified to furnish an acid-resistant support that can be cleaved at the end of a synthesis with hydrogen bromide or hydrogen fluoride. The system in present use[35] requires a saponification step which not only releases the peptide in low yield, but may also give rise to racemization.

Table II. Reaction of Poly(styrene-*co*-1% divinylbenzene) Derivatives with Amines at 25 °C

run	derivative[a]	Reagent[b]	time, h	product[c]	% yield
1	Cl-CH_2-R	100% $C_4H_9NH_2$	1	C_4H_9NH-CH_2-resin	58
2	Cl-CH_2-R	100% $C_4H_9NH_2$	18	C_4H_9NH-CH_2-resin	100
3	Boc-Val-OCH_2-R	100% $C_4H_9NH_2$	16	Boc-Val-NHC_4H_9	7.2
4	Boc-Val-OCH_2-Pam-R	100% $C_4H_9NH_2$	16	Boc-Val-NHC_4H_9	6.7
5	Boc-Val-OCH_2-R	10% $C_4H_9NH_2$	29	Boc-Val-NHC_4H_9	0.03
6	Boc-Val-OCH_2-Pam-R	10% $C_4H_9NH_2$	29	Boc-Val-NH-C_4H_9	0.05
7	Boc-Gly-OCH_2-R	5% $BzlNH_2$	29	Boc-Gly-NHBzl	0.14
8	Boc-Gly-OCH_2-Pam-R	5% $BzlNH_2$	29	Boc-Gly-NHBzl	0.33

[a] R represents polystyrene resin. [b] In runs 5–8 the amine was diluted with methylene chloride. [c] The progress of runs 1–2 was followed by elemental analyses for nitrogen and chlorine, indicating the appearance of butylaminomethyl groups and disappearance of chloromethyl groups. Boc-Val-NHC_4H_9 and Boc-Gly-NHBzl were deprotected in CF_3CO_2H and detected on the ion-exchange column of a Beckman 120B Amino Acid Analyzer.

The peptide ester of the polyacrylamide support (**16**) developed by Sheppard and co-workers[36] for peptide synthesis

16

is reported to have the same lability to acid as the peptide ester of the polystyrene support (**1**) most commonly used for solid-phase peptide synthesis.[3,4] Acylation of the polyacrylamide support with a Boc-aminoacyl-4-(oxymethyl)phenylacetic acid (**7**), rather than a Boc-aminoacyl-4-(oxymethyl)-phenylpropionic acid, should provide a peptide ester of the polyacrylamide support having the 100-fold greater acid stability displayed by the Boc-aminoacyl-4-(oxymethyl)-Pam-resins.

Conclusions

The preparation of aminomethyl-resin from unsubstituted styrene polymers allows precise control of the extent of substitution and is free from the undesirable side reactions of chloromethyl-resin. The chemically well-defined, general route to the Boc-aminoacyl-OCH_2-Pam-resins reported here represents a significant improvement over the previous, less-defined syntheses of Boc-aminoacyl-OCH_2-resins. The resulting Pam-resins show lower levels of byproducts in model peptide syntheses. The problem of the relative acidolytic labilities of the N^{α}-Boc group and the peptide–resin linkage has been solved by the 100-fold increase in the acid stability of the peptidyl-OCH_2-Pam-resin linkage, without sacrificing HF cleavage yields and without significantly increasing the susceptibility to nucleophilic side reactions.

Experimental Section

Infrared spectra were taken with a Perkin-Elmer Model 237B grating infrared spectrophotometer. Melting points were taken on

a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Model T-60 spectrometer. Elemental analyses were performed by Mr. S. T. Bella of the Microanalytical Laboratory, The Rockefeller University. The solvents used for thin-layer chromatography (TLC) (precoated 0.25-mm silica gel GF plates, Analtech) were: I, petroleum ether (bp 30–60 °C)–acetic acid, 9:1; II, petroleum ether–acetic acid (8:2); III, chloroform–acetic acid (99:1); IV, chloroform–acetic acid (95:5); V, chloroform–methanol–acetic acid (85:10:5). Spots were visualized with ultraviolet light (254 nm) followed by spraying with 0.2% ninhydrin in 1-butanol and heating. Preparative layer chromatography (PLC) was performed using 30 × 30 × 0.5 cm or 40 × 40 × 0.5 cm plates[37] prepared with silica gel PF-254 containing $CaSO_4$ (Brinkman Instruments). All solvents and bulk chemicals were reagent grade. DMF was MCB-Spectroquality and was stored over 4 Å molecular sieves. Boc-amino acids were obtained from Beckman Instruments or Chemical Dynamics. p-Tolylacetic acid, N-(hydroxymethyl)phthalimide, and bromoacetophenone were obtained from Aldrich.

Poly(styrene-co-1% divinylbenzene) beads (200–400 mesh) were purchased from Bio-Rad Laboratories. Chloromethylpoly(styrene-co-1% divinylbenzene) resin was obtained from Bio-Rad, Pierce, or Lab Systems. The materials and methods for solid phase synthesis were similar to those described elsewhere,[3,4,7] but modified as indicated.

Ion-exchange chromatography was performed using a Beckman amino acid analyzer (Model 120B or 121). The buffers were prepared from Beckman buffer concentrates. Borate buffer (pH 10) was prepared by dissolving boric acid (12 g), sodium hydroxide (8 g), and sodium chloride (35 g) in 4 L of distilled water; boric acid was added to bring the solution to pH 10.

Phthalimidomethyl-resin (4). Copoly(styrene-1% divinylbenzene) resin (200 g) was thoroughly washed[38] according to the following protocol to remove non-covalently-bound material:[39] the resin was placed in a 4-L round-bottom flask, fitted with an overhead stirrer and reflux condenser, in a water bath at 70 °C. The resin was stirred slowly with benzene (2 L) for 30 min and the solvent was removed by aspiration through a coarse sintered glass filter. This was repeated once with benzene, then twice each with 2 L of methanol, DMF, dioxane–2 N aqueous NaOH (1:1, v/v), dioxane–H_2O (1:1, v/v), dioxane–2 N aqueous HCl (1:1, v/v), and dioxane–H_2O (1:1, v/v). The resin was then rinsed with 4 L of hot methanol, 4 L of benzene, 4 L of methanol, and 4 L of CH_2Cl_2, filtered, and dried under vacuum. The washed resin and N-(hydroxymethyl)phthalimide (90 mol % pure by NMR[46]) (8.14g, 41 mmol) were placed in a three-neck round-bottom flask (5 L) equipped with an overhead stirrer. CF_3COOH–CH_2Cl_2 (2 L) (1:1, v/v) was added. The resin was suspended by rapid stirring and trifluoromethanesulfonic acid (18 mL, 0.20 mol) was slowly added. Stirring was continued at room temperature. The amidoalkylation reaction was followed by IR of KBr pellets of washed resin samples (~10 mg). The substitution of the resin is given approximately by: ([intensity 1720 cm^{-1}]/[intensity 1601 cm^{-1}]) × 0.17 = mmol/g. The reaction was allowed to proceed to completion as indicated by no further change in the IR spectrum (less than 6 h), and the resin was filtered and washed with: CF_3COOH–CH_2Cl_2 (1:1, v/v) (4 L), CH_2Cl_2 (8 L), and ethanol (8 L). The resin was dried under vacuum overnight to give **4.** Anal.: N, 0.28% (0.20 mmol N/g).

Aminomethyl-resin (5). Resin **4** (180 g) was refluxed without stirring for 16 h in ethanol (2 L) containing 5% hydrazine (Eastman 95 + %). The resin was filtered hot and washed (with stirring 5–10 min each wash) with boiling ethanol (4 × 2 L) and methanol (4 × 2 L). The product was dried under vacuum to give **5,** which contained 0.26% N (0.19 mmol N/g) by elemental analysis, 0.22 mmol of NH_2/g by picric acid titration,[40] and no carbonyl groups by IR. Examination of the CH_2Cl_2-swollen resin under the microscope showed the beads to be identical in appearance with the starting polystyrene resin.

4-(Bromomethyl)phenylacetic Acid (11). Prepared by photobromination.[19] p-Tolylacetic acid (30 g, 0.20 mol) was dissolved in CCl_4 (400 mL) and brought to reflux with magnetic stirring in a two-neck round-bottom flask (2 L) fitted with a reflux condenser and a 250-mL addition funnel. Bromine (14.5 mL, 0.56 mol) in CCl_4 (150 mL) was added slowly over a 1–2 h period to the refluxing solution, while the reaction was illuminated with a 150-W tungsten lamp placed 6 in. from the flask. The rate of reaction can be estimated from the white fuming HBr evolved (*Caution:* these fumes should be led directly to a hood vent), and controlled by the degree of illumination. The ambient light level may be sufficient to sustain the reaction. When HBr evolution had ceased (typically, overnight) the reaction mixture was cooled to room temperature. The insoluble product was collected by filtration and washed with CCl_4 (6 × 200 mL). The off-white solid was recrystallized from hot benzene (2 L) by addition of hexane (about 200 mL) to turbidity to give **11** (23.4 g, 51% yield): mp 177–178 °C; NMR (Me_2SO-d_6) 3.55 (s, 2 H, CH_2CO), 4.67 (s, 2 H, $BrCH_2$), and 7.30 ppm (m, 4 H, p-C_6H_4). Anal. Calcd. for $C_9H_9O_2Br$: C, 47.18; H, 3.96; Br, 34.89. Found: C, 47.26; H, 4.01; Br, 34.59.

4-(Bromomethyl)phenylacetic Acid Phenacyl Ester (9). Triethylamine (8.49 mL, 60.6 mmol) and bromoacetophenone (12.05 g, 60.6 mmol) were dissolved in ethyl acetate (450 mL). **11** (13.89 g, 60.6 mmol) was added in seven equal portions over a 3-h period to the stirred solution at 40–50 °C. Stirring was continued for a further 2 h at the same temperature. Precipitated Et_3N·HBr was removed by filtration, and the ethyl acetate solution was washed with aqueous solutions (4 × 50 mL each) of 10% citric acid, saturated sodium chloride, saturated sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over anhydrous magnesium sulfate and freed of solvent by rotary evaporation under reduced pressure. The residue was crystallized from CH_2Cl_2–petroleum ether (bp 30–60 °C) (1:3, v/v) to give **9** (8.07 g, 40% yield) as fine white crystals: mp 85–87 °C; TLC, pure (100 μg loading, solvent II); NMR ($CDCl_3$) 3.83 (s, 2 H, CH_2COO), 4.50 (s, 2 H, $BrCH_2$), 5.37 (s, 2 H, OCH_2CO), 7.38 (apparent s, 4 H, p-C_6H_4), and 7.7 ppm (m, 5 H, C_6H_5). The presence of dimer, 4′-($BrCH_2$)$PhCH_2CO$-4-(OCH_2)$PhCH_2COOCH_2COPh$, would be shown by NMR peaks at 3.67(s) and 5.17 ppm (s) with a detection level of <1 mol%. Anal. Calcd, for $C_{17}H_{15}BrO_3$: C, 58.80; H, 4.35; Br, 23.02. Found: C, 58.32; H, 4.26; Br, 23.26.

Boc-valyl-4-(oxymethyl)phenylacetic Acid Phenacyl Ester (10a). The valine compound is typical. Boc-L-Val (3.10 g, 14.3 mmol), DCHA (2.82 mL, 14.4 mmol), and **9** (2.50 g, 7.3 mmol) were reacted in 60 mL of DMF for 4 h at 50 °C and overnight at room temperature. Precipitated DCHA·HBr was removed by filtration, and the filtrate was freed of solvent by rotary evaporation under high vacuum. The yellow residue was dissolved by stirring for 2 h in EtOAc (450 mL), and insoluble DCHA·HBr was removed by filtration. The ethyl acetate solution was thoroughly extracted with 10% aqueous citric acid (3 × 75 mL) to remove residual DCHA, water (3 × 75 mL), pH 9.5 buffer (one part 0.5 M K_2CO_3 plus two parts 0.5 M $NaHCO_3$) (10 × 75 mL) to remove excess Boc-Val, and water (3 × 75 mL). Removal of all traces of excess Boc-amino acid is crucial and can be monitored by TLC. After drying over $MgSO_4$, the EtOAc was removed by rotary evaporation to give a white solid which was dried under vacuum: weight 3.02 g (theoretical for 7.3 mmol, 3.52 g); TLC (benzene–HOAc, 95:5, v/v) showed **10a,** R_f 0.45, and several minor (<1%) UV-active components of lower R_f. No **9,** R_f 0.9, and no free Boc-Val, R_f 0.4, were detected. This product was suitable for reduction to **7a** as described below. Products of comparable purity containing Lys(Z), Asp(OBzl), Ser(Bzl), and Met were similarly prepared in near-quantitative yields.

An analytical sample of the valine compound was purified by PLC (solvents I, and III) yielding hard, amorphous solid **10a:** $[\alpha]^{24}_D$ −18.5° (c 2, CH_3OH); NMR ($CDCl_3$) 0.97 (m, 6 H, $(CH_3)_2$), 1.53 (s, 9 H, t-Bu), 2.18 (m, 1 H, $C_\beta H$), 3.87 (s, 2 H, CH_2COO), 4.28 (m, 1 H, α-CH), 5.05 (br d, J = 8 Hz, 1 H, NH), 5.21 (s, 2 H, OCH_2), 5.40 (s, 2 H, OCH_2CO), 7.38 (apparent s, 4 H, p-C_6H_4), and 7.72 ppm (m, 5 H, C_6H_5). Anal. Calcd for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90. Found: C, 67.09; H, 6.90; N, 2.78.

Boc-valyl-4-(oxymethyl)phenylacetic Acid (7a). Crude **10a** (3.02 g, 6.25 mmol), purified as described above, was dissolved in 90 mL of HOAc–H_2O (85:15, v/v), and the NMR spectrum in the 2.4–6-ppm region was recorded. Zinc dust (9.64 g, 147 mmol) was added and the suspension was stirred vigorously at room temperature. [Zinc dust (40 g) had previously been acid washed, as follows: 1 N aqueous HCl (6 × 150 mL; 2 min each), H_2O (6 × 150 mL; 1 min), EtOH (6 × 150 mL; 1 min), Et_2O (6 × 150 mL; 1 min). After 5 min aspiration, it was stored in a screw-capped brown bottle. The activity did not change significantly after more than 6 months storage at room temperature.] The reduction was conveniently monitored by NMR of aliquots of the suspension, which were subsequently returned to the reaction vessel. The phenacyl ester CH_2 singlet at 5.4 ppm gradually disappeared with concomitant formation of acetophenone at 2.85 ppm (s, 3 H, CH_3). Similarly, the phenylacetic acid ester singlet at 3.85 ppm disappeared and was replaced by the singlet due to the free acid, at 3.65 ppm. The reduction was always complete within 6 h. No cleavage (<5%) of the benzyl ester bond occurred in 72 h under these conditions. Only ~15% of the N^α-Boc group was removed after 72 h. Therefore, after 6 h only 1–2% of product would be deprotected and removed in the workup. After 6 h the zinc was removed by filtration and washed with 15 mL of 85% HOAc in H_2O. The filtrate, 105 mL, was placed in a separatory funnel with 200 mL of Et_2O, and then 170 mL of water was added, forming a biphasic system. The aqueous phase was titrated in the presence of the Et_2O with 6 N HCl to pH 1–1.5

Table III

Boc-L-Lys(Z)-OCH_2PhCH_2COOH·CHA	(**7b**)	83–93 °C dec	Calcd for $C_{34}H_{49}N_3O_8$:	C, 65.05; H, 7.87; N, 6.69
			Found:	C, 65.29; H, 8.00; N, 6.47
Boc-L-Asp(OBzl)-OCH_2PhCH_2COOH·CHA	(**7c**)	136–138 °C	Calcd for $C_{31}H_{42}N_2O_8$:	C, 65.24; H, 7.42; N, 4.91
			Found:	C, 65.32; H, 7.47; N, 5.01
Boc-L-Ser(Bzl)-OCH_2PhCH_2COOH·CHA·$1.5H_2O$	(**7d**)	125–128 °C	Calcd for $C_{30}H_{44}N_2O_8$:	C, 63.30; H, 7.96; N, 4.92
			Found:	C, 63.04; H, 7.69; N, 5.11
Boc-L-Met-OCH_2PhCH_2COOH·CHA	(**7e**)	hard oil	Calcd for $C_{25}H_{40}N_2O_6S$:	C, 60.45; H, 8.12; N, 5.64
			Found:	C, 60.31; H, 8.02; N, 5.27

(narrow range paper). After vigorous shaking, the Et_2O (product-containing) layer was separated and the aqueous phase was extracted a second time with 200 mL of Et_2O. The combined ether layers were backwashed with five 200-mL portions of water to remove the bulk of the acetic acid.

TLC showed that more than 99% of the product was in the combined Et_2O layers, together with acetophenone. Ether was removed by rotary evaporation under reduced pressure. The acetic acid remaining was removed by rotary evaporation, at 40 °C, under high vacuum. Residual traces of acetic acid were removed as an azeotrope by the evaporation of six 20-mL portions of benzene. The residue was pumped for 16 h over KOH pellets. Removal of all acetic acid is critical to avoid contamination of the final product with this terminating impurity. The absence of acetic acid (to <1 mol %) can be determined by NMR at this stage. The residue was dissolved in 100 mL of Et_2O and filtered to remove a small (~100 mg) amount of insoluble material. The salt was formed by titration of the Et_2O solution with CHA (or DCHA) to a pH 8 end point (moist narrow range paper). After 72 h at 4 °C white crystals of the CHA salt of **7a** were recovered and washed with Et_2O–petroleum ether: weight 1.85 g (4.0 mmol); yield 55% based on **9**; mp 148–152 °C (lit.[9] 153–154 °C). A second crop was obtained: 0.20 g; mp 138–143°C. Recrystallization of the combined crops gave: 1.80 g (52%); mp 150–152 °C; NMR ($CDCl_3$) 0.90 (m, 6 H, $(CH_3)_2$), 0.8–1.8 (m, 10 H, CHA methylenes), 1.48 (s, 9 H, *t*-Bu), 2.15 (m, 1 H, β-CH), 2.53 (m, 1 H, CHA methine), 3.47 (s, 2 H, CH_2CO), 4.20 (m, 1 H, α-CH), 5.03 (br d, J = 8 Hz, 1 H, NH), 5.13 (s, 2 H, OCH_2), 7.0 (br s, 3 H, NH_3), and 7.27 ppm (apparent s, 4 H, *p*-C_6H_4); TLC (petroleum ether (bp 30–60 °C)–HOAc, 96:4, v/v, five passes, 100 μg) showed: the desired **7a**, apparent R_f 0.4; CHA, R_f 0, no (<0.1%) Boc-Val-OH, apparent R_f 0.9; no acetophenone (high R_f on initial pass). Anal. Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.66; H, 8.49; N, 5.84.

Other compounds prepared in the same way in good yield are given in Table III. Satisfactory analytical data (±0.4% for C, H, N; TLC purity; expected NMR) were obtained for all the compounds listed. For **7d**, the 1.5 mol of H_2O was seen by ^1H NMR in $CDCl_3$.

Boc-aminoacyl-4-(oxymethyl)-Pam-resin (8). The CHA or DCHA salt of **7** was first converted to the free acid as follows. The CHA salt of **7** (4.4 mmol) was suspended in 150 mL of water and 150 mL of Et_2O. The calculated amount of 3 N HCl was added with vigorous shaking. The aqueous layer was titrated to pH 1–2 (narrow range paper) by the addition of further small amounts of 3 N HCl. The Et_2O layer was separated, and the aqueous layer was extracted with 2 × 150 mL of Et_2O. The combined Et_2O layers were backwashed with 100 mL of water. TLC of the Et_2O and aqueous solutions showed quantitative extraction of **7** into the Et_2O, while all CHA remained in the aqueous phase. After drying over $MgSO_4$, the Et_2O was evaporated and the free **7** was taken up in 100 mL of CH_2Cl_2 and added to aminomethyl-resin (**5**) (10 g, 2.2 mmol). After 5 min of shaking DCC (0.91 g, 4.4 mmol) in 100 mL of CH_2Cl_2 was added and the mixture was shaken for 16 h at room temperature. The resin was filtered and washed with 6 × 200 mL of CH_2Cl_2. The extent of coupling was determined by picric acid titration[40] of free amino groups. If necessary, residual amino groups were acetylated with 200 mL of acetic anhydride–pyridine (1:1, v/v) for 2 h. The resin was filtered and washed with CH_2Cl_2, CH_2Cl_2–HOAc (1:1), HOAc, 2-propanol, and CH_2Cl_2, and vacuum dried to furnish **8** with a loading of 0.21 mmol/g (amino acid analysis,[41] picrate after deprotection).

Alternative Preparation of 7a. 7a was prepared by direct reaction of Boc-L-Val DCHA salt with 4-($BrCH_2$)$PhCH_2COOH$, as previously described.[9] After PLC, valine-containing **7a** was obtained as the CHA salt (3.08 g, 53% yield): mp 149–150 °C; $[\alpha]^{24}_D$ −23.0° (*c* 2, CH_3OH). Anal. Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.72; H, 8.70; N, 5.99. The dimeric Boc-L-Val-4-(OCH_2) $PhCH_2CO$-4-(OCH_2)$PhCH_2COOH$ was also isolated: mp 89–91 °C; NMR ($CDCl_3$) 0.95 (m, 6 H, $(CH_3)_2$), 1.48 (s, 9 H, *t*-Bu), 2.18 (m, 1 H, β-CH), 3.66 and 3.68 (apparent (d, 4 H, $(CH_2CO)_2$), 4.25 (m, 1 H, $C_\alpha H$), 5.15 and 5.18 (apparent d, 4 H, $(OCH_2)_2$), and 6.98 ppm (apparent s, 8 H, (*p*-$C_6H_4)_2$). Anal. Calcd for $C_{28}H_{35}NO_8$: C, 65.48; H, 6.87; N, 2.73. Found: C, 65.36; H, 6.13; N, 2.67.

4-(Bromomethyl)phenylacetic Acid *N*-Hydroxysuccinimide Ester (17): from **11**, *N*-hydroxysuccinimide, and DCC by the method of Anderson et al.[42] The crude product was crystallized from 2-propanol to give white needles of **17**: yield 68%; mp 148–149.5 °C; NMR ($CDCl_3$) 2.87 (s, 4 H, CH_2CH_2), 3.97 (s, 2 H, CH_2COO), 4.51 (s, 2 H, $BrCH_2$), and 7.40 ppm (apparent s, 4 H, *p*-C_6H_4). Anal. Calcd for $C_{13}H_{12}BrNO_4$: C, 47.87; H, 3.70: N, 4.29; Br, 24.53. Found: C, 47.79; H, 3.72; N, 4.63; Br, 24.40.

Boc-valyl-4-(oxymethyl)phenylacetic Acid *N*-Hydroxysuccinimide Ester (18). An authentic sample was prepared from the reaction of **7a**, *N*-hydroxysuccinimide, and DCC by the general method of Anderson et al:[42] yield 48%; mp 101–102 °C; $[\alpha]^{24}_D$ −17.9° (*c* 2, CH_3OH); NMR ($CDCl_3$) 0.95 (m, 6 H, $(CH_3)_2$), 1.50 (s, 9 H, *t*-Bu), 2.13 (m, 1 H, $C_\beta H$), 2.85 (s, 4 H, CH_2CH_2), 3.95 (s, 2 H, CH_2COO), 4.23 (m, 1 H, $C_\alpha H$), 5.00 (br d, J = 10 Hz, 1 H, NH), 5.15 (s, 2 H, OCH_2), and 7.35 ppm (apparent s, 4 H, *p*-C_6H_4). Anal. Calcd for $C_{23}H_{30}N_2O_8$: C, 59.73; H, 6.54; N, 6.06. Found: C, 59.66; H, 6.54; N, 6.02.

The reaction of Boc-L-ValOCs[22] and **17** in DMF gave a multiplicity of products (TLC, system I). The presence of **18** was detected, but preliminary attempts to separate the pure compound were unsuccessful and the preparation was abandoned.

4-(Acetoxymethyl)phenylacetic Acid (13). Sodium acetate and **11** were reacted as previously described using the 4-($ClCH_2$)-$PhCH_2COOH$.[9] Recrystallization from hot water gave **13**: yield 77%; mp 85–86 °C (lit.[9] mp 84–86 °C); TLC pure (R_f 0.35, twice developed in II); NMR ($CDCl_3$) 2.23 (s, 3 H, CH_3CO), 3.75 (s, 2 H, CH_2CO), 5.20 (s, 2 H, OCH_2), 7.40 (apparent s, 4 H, *p*-C_6H_4), and 10.67 ppm (br s, 1 H, COOH).

4-(Acetoxymethyl)-Pam-resin (14). A solution of **13** (3.64 g, 17.5 mmol) in 250 mL of CH_2Cl_2 was shaken with **5** (25.0 g, 8.94 mmol NH_2) for 5 min. DCC (3.60 g, 17.5 mmol) was added in 50 mL of CH_2Cl_2 and the suspension was shaken at room temperature for 3 h. The resin **14** was filtered and washed with 4 L of CH_2Cl_2. Picric acid titration[40] gave 0.0006 mmol of NH_2/g. Strong carbonyl absorptions were observed in the IR spectrum at 1740 (ester) and 1680 cm^{-1} (amide).

4-(Bromomethyl)-Pam-resin (12). A. From HBr Cleavage of 14. A saturated solution of HBr in acetic acid was prepared by bubbling HBr through a trap containing anisole–acetic acid–CH_2Cl_2 and then into 10:1 acetic acid–anisole (55 mL) for several hours. The cleavage solution was added to **14** (5.00 g, 1.59 mmol) and the suspension was shaken for 2 h. The suspension was filtered and the resin was washed with acetic acid (3 × 50 mL), methanol (3 × 50 mL), and dichloromethane (10 × 50 mL) and dried under vacuum to give **12.** The infrared spectrum of the resin showed a weak residual carbonyl absorption at 1740 cm^{-1} (ester) and a strong band at 1680 cm^{-1} (amide).

B. From 4-(Bromomethyl)phenylacetic acid (11) and Aminomethyl-resin (5). 4-(Bromomethyl)phenylacetic acid (**11**; 2.29 g, 10.0 mmol) and DCC (1.03 g, 5.00 mmol) were allowed to react in 25 mL of tetrahydrofuran at 5 °C for 1 h. The suspension was filtered and the filtrate was added to **5** (5.00 g, 1.10 mmol). The reaction mixture was shaken at room temperature for 1 h. The suspension was filtered and the resin was washed with tetrahydrofuran, CH_2Cl_2, CH_2Cl_2–HOAc (1:1, v/v), HOAc, ethanol, and methanol. The resin **12** was dried under vacuum. Anal.: N, 0.25% (0.18 mmol N/g); Br, 1.62% (0.20 mmol Br/g).

Boc-aminoacyl-4-(oxymethyl)-Pam-resin (8) from Resin 12. The cesium salts[22] (2 equiv) of Boc-Gly, Boc-L-Phe, and Boc-L-Val were allowed to react with resin **12** (0.20 mmol of Br/g), prepared from **11** and **5**, in DMF for 36 h at room temperature (Scheme IV). The Boc-aminoacyl-OCH_2-Pam-resins so produced had loadings of 0.160 mmol of Gly/g, 0.184 mmol of Phe/g, and 0.175 mmol of Val/g as determined by acid hydrolysis for 6 h (130 °C) in HCL–propionic acid (1:1, v/v)[41] and subsequent amino acid analysis.

In a similar manner, Boc-Val-OCs was allowed to react with resin

12 (~0.32 mmol of Br/g), prepared from **14**, yielding Boc-Val-OCH_2-Pam-resin (Scheme V) having a loading of 0.26 mmol of Val/g by amino acid analysis.

Test for Racemization. Synthesis of Boc-Leu-Val-OCH_2-Pam-resin. Boc-Val-OCH_2-Pam-resin (**8a**; 0.200 g, 0.0432 mmol) was placed in a 6-mL reaction vessel. The resin was suspended in trifluoroacetic acid–CH_2Cl_2 (1:1, v/v) and shaken for 1 h. The resin was filtered, washed with CH_2Cl_2, neutralized with 5% ethyldiisopropylamine in CH_2Cl_2, washed with CH_2Cl_2, and coupled for 30 min with 4 equiv of Boc-Leu and 4 equiv of DCC in 4 mL of CH_2Cl_2. The resin was filtered, washed with CH_2Cl_2, CH_2Cl_2–HOAc (1:1, v/v), HOAc, ethanol, and methanol, and dried under vacuum.

A sample (51 mg) of the Boc-Leu-Val-OCH_2-Pam-resin was shaken in 2 mL of trifluoroacetic acid–CH_2Cl_2 (1:1, v/v) containing 20 equiv of trifluoromethanesulfonic acid[43] for 30 min. The cleavage solution was filtered and the resin was washed with (3 × 2 mL) trifluoroacetic acid–CH_2Cl_2 (1:1 v/v). The pooled filtrates were evaporated in vacuo and the residue was dissolved in 10 mL of pH 4.25 sodium citrate buffer (0.2 N). A 1-mL sample of this solution was injected into the long column (0.9 × 58 cm; AA-15 sulfonated polystyrene) of a Beckman 120B amino acid analyzer and eluted with pH 4.25 citrate buffer (61 mL/h; 57 °C). A large peak corresponding to L-Leu-L-Val (153 min) was seen, whereas no detectable peak (<0.1%) was observed at or near the elution position of L-Leu-D-Val (136 min).[26]

Synthesis of Leu-Ala-Gly-Val. The following protocol was used for the syntheses of the model tetrapeptide. Boc-L-Val-OCH_2-Pam-resin (**8a**; 1 g) was placed in a reaction vessel on a shaker and treated as follows for the incorporation of each residue: (1) washed with 20 mL of CH_2Cl_2 (3 × 1 min); (2) shaken with 20 mL of trifluoroacetic acid–CH_2Cl_2 (1:1, v/v) for 30 min; (3) washed with 20 mL of CH_2Cl_2 (6 × 1 min); (4) shaken with 20 mL of 5% ethyldiisopropylamine in CH_2Cl_2 for 5 min: (5) washed with 20 mL of CH_2Cl_2 (3 × 1 min); (6) repeat step 4; (7) repeat step 5; (8) shaken with Boc-Gly (4 equiv) in 15 mL of CH_2Cl_2 for 5 min; (9) without filtration, DCC (4 equiv) in 5 mL of CH_2Cl_2 was added and shaken for 30 min; (10) washed with 20 mL of CH_2Cl_2 (3 × 1 min). The cycle was repeated with Boc-L-Ala, then with Boc-L-Leu. In a double-coupling synthesis, steps 6–10 were repeated in each cycle. The Boc-Leu-Ala-Gly-Val-OCH_2-Pam-resin was washed with CH_2Cl_2–HOAc (1:1 v/v), HOAc, 2-propanol, and CH_2Cl_2, and vacuum dried. The peptide was cleaved from the resin with HF–anisole (9:1, v/v) at 0 °C for 30 min. The cleaved material was taken up in 5% HOAc, filtered, evaporated to dryness, and dissolved in water for analysis. The sample was injected onto the 0.9 × 58 cm column (AA-15 cation exchange resin) of a Beckman 120B amino acid analyzer and eluted (61 mL/h; 57 °C) with pH 3.49 citrate buffer (0.2 N in sodium). The sample was intentionally overloaded (about 4 μmol of peptides) so that less than one part per 1000 of ninhydrin-positive components could be detected.[28]

The following resins were used for syntheses of Leu-Ala-Gly-Val.

I. 8a Obtained from 5 and 7a (Scheme II). Analysis showed the desired tetrapeptide as 98.0 mol % of the unpurified peptide product, together with 0.10–0.22 mol % of each single-deletion peptide. A double coupling synthesis gave the tetrapeptide as 99.2 mol % and reduced to <0.06 mol% each of the deletion peptides.

II. 8a Obtained from Boc-Val-OCs and 12 (Scheme IV). Analysis showed the tetrapeptide as 97.3 mol % of the unpurified peptide product, together with 0.32–0.57 mol % of each single-deletion peptide.

III. 8a Obtained from 14 (Scheme V). A double-coupling synthesis was performed. Analysis showed the tetrapeptide as 99.2 mol % of the unpurified peptide product, together with 0.06–0.10 mol % of each single-deletion peptide.

Boc-valyl-4-(oxymethyl)-Pam-benzene (15). Compound **18** (0.93 g, 2.00 mmol) and benzylamine (0.24 mL, 2.2 mmol) were reacted in ethyl acetate (15 mL) for 16 h at room temperature. The product was worked up in the usual manner and crystallized from ethyl acetate–petroleum ether (bp 30–60 °C) to give 0.56 g (62% yield) of **15**: mp 101.5–103 °C; $[\alpha]^{24}_D$ −21.6° (c 2, CH_3OH); NMR ($CDCl_3$) 0.95 (m, 6 H, $(CH_3)_2$), 1.50 (s, 9 H, t-Bu), 2.15 (m, 1 H, β-CH), 3.65 (s, 2 H, CH_2CO), 4.27 (m, 1 H, α-CH), 4.20 (d, J = 6 Hz, 2 H, N-CH_2), 5.02 (br d, 1 H, urethane NH), 5.18 (s, 2 H, OCH_2), 5.82 (br s, 1 H, benzylamide NH), and 7.32 ppm (m, 9 H, aryl). Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.69; H, 7.54; N, 6.16. Found, C, 68.65; H, 7.41; N, 6.08.

Stability of Boc-amino acid-resins and Boc-valyl-4-(oxymethyl)-Pam-benzene (15) in Refluxing Trifluoroacetic Acid. Boc-amino acid-resin (50 mg) was placed in a 25-mL round-bottom flask equipped with a water condenser and drying tube. Anhydrous trifluoroacetic acid (10 mL) was added and the suspension was refluxed. At a given time the resin was filtered and washed with trifluoroacetic acid. The combined filtrates were evaporated in vacuo and the residue was dissolved in water for amino acid analysis. The extent of cleavage was measured for the Boc-aminoacyl-OCH_2-Pam-resins and compound **15** at 2, 4, and 6 h. Cleavage of Boc-Val-OCH_2-resin was measured at 15, 30, and 45 min. The results are summarized in Table I.

HF Cleavage Yields. Boc-Gly-OCH_2-Pam-resin (50.5 mg, 0.0081 mmol), Boc-L-Phe-OCH_2-Pam-resin (59.1 mg, 0.0096 mmol), Boc-L-Val-OCH_2-Pam-resin (54.7 mg, 0.0096 mmol), and Boc-Leu-Ala-Gly-Val-OCH_2-Pam-resin (106.9 mg, 0.0208 mmol) were cleaved with 10 mL of HF plus 1 mL of anisole for 32 min at 0 °C. After evaporation of the HF, residual anisole was removed by two 25-mL Et_2O rinses. The products were taken up by rinsing with 20% HOAc (2 × 25 mL) and HOAc (2 × 25 mL) After filtration, the solvent was evaporated and the residue was taken up in H_2O for analysis. The resin remaining after the HF cleavage was hydrolyzed for 6 h (130 °C) in HCl–propionic acid[41] to determine the residual amino acid content. Observed recoveries from HF cleavage were (residual amino acid shown in parentheses): Gly, 106% (4%); Phe, 82% (9%); Val, 88% (6%); Leu-Ala-Gly-Val, 94%.

Boc-valine-butylamide. Boc-Val (1.08 g, 5.00 mmol) and p-nitrophenyl trifluoroacetate[44] (1.41 g, 6.00 mmol) were reacted in dry pyridine (4 mL) for 1.5 h at room temperature. Water (0.018 mL, 1.00 mmol) was then added to destroy the excess p-nitrophenyl trifluoroacetate. After 5 min, n-butylamine was added (0.99 mL, 10 mmol) and the solution was allowed to stand overnight. The solvent was removed in vacuo and the resulting oil was worked up in the usual manner. A crystallization of the title compound from acetone–H_2O gave white needles (0.399 g, 29% yield): mp 113–116 °C; TLC (Solvent V) R_f 0.82; $[\alpha]^{25}_D$ − 22.7° (c 2.2, CH_3OH); NMR ($CDCl_3$) 1.00 (m, 9 H, Val γ-$(CH_3)_2$ and n-BuCH_3), near 1.4 (m, 4 H, n-Bu β,γ-CH_2CH_2), 1.50 (s, 9 H, t-Bu), 2.10 (m, 1 H, $C_\beta H$), 3.30 (q, J = 6 Hz, 2 H, NCH_2), 3.87 (m, 1 H, $C_\alpha H$), 5.17 (br d, J = 8 Hz, 1 H, urethane NH), and 6.17 ppm (br s, 1 H, CONHBu). Anal. Calcd for $C_{14}H_{28}N_2O_3$: C, 61.73; H, 10.36; N, 10.29. Found: C, 61.65; H, 10.24; N, 10.19.

Treatment of Chloromethyl-resin and Boc-amino acid-resins with Amines. A. Reaction with n-Butylamine. Chloromethylpoly(styrene-co-1% divinylbenzene) resin (Pierce, 0.69 mmol of Cl/g of resin) was suspended in n-butylamine (25 mL/g of resin) and either shaken at 25 °C (1, 18 h) or refluxed (1 h). The suspension was filtered and the resin was washed with dimethylformamide, dichloromethane, 2-propanol, and ethanol, and vacuum dried. The resin treated with n-butylamine for 1 h (25 °C) contained 0.40 mmol of N/g of resin and 0.30 mmol of Cl/g of resin. The 18-h sample (25 °C) contained 0.71 mmol of N/g of resin and no Cl. Similarly, a resin refluxed in n-butylamine (1 h) contained 0 72 mmol of N/g of resin and no Cl. See Table II (runs 1–2).

Boc-Val-resin (0.100 g) was suspended in 4 mL of 100% n-$C_4H_9NH_2$ (Table II, runs 3 and 4) or 10% (v/v) n-$C_4H_9NH_2$–CH_2Cl_2 (Table II, runs 5 and 6) and shaken at 25 °C. At a given time the suspension was filtered and the resin was washed with dichloromethane. The pooled filtrates were evaporated in vacuo and the residue was treated with trifluoroacetic acid (25 °C) for 30 min. The trifluoroacetic acid was evaporated in vacuo and the residue was dissolved in water (5 mL) for injection into the long column (0.9 × 58 cm AA-15 cation-exchange resin) of the Beckman 120B amino acid analyzer. The column was eluted with borate (pH 10) buffer at 57 °C (61 mL/h). A standard was prepared by treating Boc-Val-NHC_4H_9 with trifluoroacetic acid and removing trifluoroacetic acid in vacuo. The resulting valine n-butylamide eluted at 49 min using the ion-exchange column just described.

B. Reaction with Benzylamine. Boc-Gly-resin (0.100 g) was suspended in 5% (v/v) benzylamine–dichloromethane (Table II, runs 7 and 8) and treated as described for Boc-Val-resin. Glycine benzylamide[45] eluted at 86 min under the conditions of ion-exchange chromatography described for valine n-butylamide. The results obtained from treatment of the polystyrene derivatives with amines are summarized in Table II.

Acknowledgment. We wish to thank Roland Koestner for technical assistance in this work.

Registry No.—N-(Hydroxymethyl)phthalimide, 118-29-6; copoly(styrene–divinylbenzene, 9003-70-7; p-tolylacetic acid, 622-47-9; 4-(bromomethyl)phenylacetic acid, 13737-36-5; bromoacetophenone, 70-11-1; 4-(bromomethyl)phenylacetic acid phenacyl ester, 66270-97-1; Boc-L-Val, 13734-41-3; Boc-Valyl-4-(oxymethyl)phenylacetic acid phenacyl ester, 66402-58-2; Boc-Valyl-4-(oxymethyl)phenylacetic acid CHA salt, 66270-98-2; Boc-L-Lys(Z)-OCH_2PhCH_2COOH CHA salt, 66271-00-9; BOC-L-Asp(OBzl)OCH_2PhCH_2COOH CHA salt,

66271-02-1; Boc-L-Ser(Bzl)-OCH_2PhCH_2COOH CHA salt, 66271-04-3; Boc-L-Met-OCH_2PhCH_2COOH CHA salt, 66271-06-5; Boc-L-Lys(Z)-$OCH_2C_6H_4$-*p*-CH_2COOH_2COPh, 66271-07-6; Boc-L-Asp(OBzl)-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-08-7; Boc-L-Ser(Bzl)-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-09-8; Boc-L-Met-$OCH_2C_6H_4$-*p*-CH_2COOCH_2COPh, 66271-10-1; Boc-Val-$OCH_2C_6H_4$-*p*-$CH_2CONHCH_2Ph$, 66271-11-2; Boc-L-Val DCHA salt, 16944-17-5; Boc-L-Val-4-$(OCH_2)PhCH_2CO$-4-$(OCH_2)PhCH_2COOH$, 66271-12-3; *N*-hydroxysuccinimide, 6066-82-6; 4-(bromomethyl)-phenylacetic, acid *N*-hydroxysuccinimide ester, 66271-13-4; Boc-Valyl-4-(oxymethyl)phenylacetic acid *N*-hydroxysuccinimide ester, 66271-14-5; 4-(acetoxymethyl)phenylacetic acid, 61165-81-9; Boc-Gly Cs salt, 42538-64-7; Boc-L-Phe Cs salt, 42538-61-4; Boc-L-Val Cs salt, 42538-62-5; Boc-Leu, 13139-15-6; L-Leu-L-Val, 13588-95-9; Boc-Gly, 4530-20-5; Boc-L-Ala, 15761-38-3; Leu-Ala-Gly-Val, 17195-26-5; benzylamine, 100-46-9; *p*-nitrophenyltrifluoroacetate, 658-78-6; butylamine, 109-73-9; Boc-Valine butylamide, 66271-15-6; Boc-Gly-NHBzl, 19811-52-0.

References and Notes

(1) Supported in part by Grant AM 01260 from the U.S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation. M. E. was the recipient of a fellowship from the Deutsche Forschungsgemeinschaft.
(2) Abbreviations used: Boc, *tert*-butyloxycarbonyl; CHA, cyclohexylamine; DCC, dicyclohexylcarbodiimide; DCHA, dicyclohexylamine; DMF, *N,N*-dimethylformamide; KelF-g-styrene, radiation-induced graft polymer of styrene on solid poly(trifluorochloroethylene); NMR, nuclear magnetic resonance; Pam, phenylacetamidomethyl; PLC, preparative layer chromatography; R, resin; TLC, thin-layer chromatography. Other nomenclature and symbols follow the Tentative Rules of the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241,** 2491 (1966); **242,** 555 (1967); **247,** 977 (1972).
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Synthesis of Oxysanguinarine

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Base-catalyzed condensation of the homophthalate ester **14** with the imine **15** supplied the lactam amide **16.** This compound was saponified to the acid **17** which was homologated by an Arndt–Eistert sequence to the ester **19.** Hydrolysis and acid-catalyzed cyclization provided the keto lactam **21.** Acid dehydration of the lactam alcohol **22,** derived from reduction of **21,** was accompanied by air oxidation to provide the desired alkaloid oxysanguinarine (**23**).

A number of aromatic benzophenanthridine alkaloids possess interesting biological activity. Nitidine (**1**) and fagaronine (**2**) have shown anticancer activity,[1] while sanguinarine (**3**), chelerythrine (**4**), and chelirubine (bocconine) (**5**) are nematocides.[2]

The aim of the present study was to synthesize a naturally occurring aromatic benzophenanthridine, namely oxysanguinarine (**23**),[3] through a route based on the previously reported finding that base-catalyzed condensation of diethyl glutaconate with *N*-benzylidenemethylamine yields lactam **6**.[4] The first hurdle was to prepare the homophthalic ester **14,** which was to be condensed with piperonylidenemethylamine (**15**) to afford such lactams as **16, 17,** or **18.** Homologation of the acid **17** to the acid **20,** followed by intramolecular Friedel–Crafts acylation, would then afford keto lactam **21,** which would be readily convertible into oxysanguinarine (**23**).

An eight-step sequence to the homophthalic ester **14** was developed which parallels to some extent, but is superior to, that recorded by Haworth and co-workers for the construction of the corresponding homophthalic acid **13**.[5] Doebner con-

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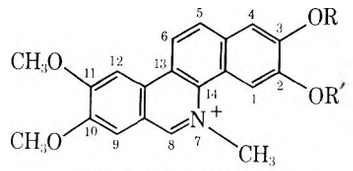
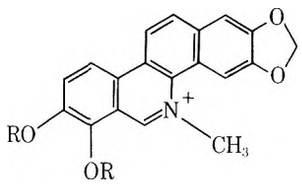
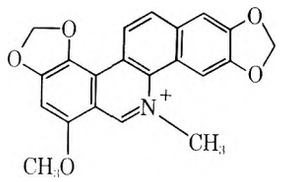


1, R + R′ = CH_2
2. R = H; R′ = CH_3

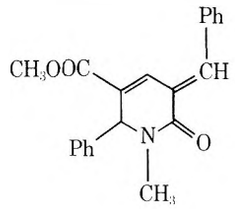


3. R + R′ = CH_2
4. R = CH_3



5

densation of piperonal with malonic acid in refluxing pyridine gave the cinnamic acid **7** in 90% yield. Catalytic hydrogenation of the sodium salt of **7** in water using 5% palladium on carbon furnished, upon acidification, piperonylacetic acid (**8**) in 95% yield. Attempted cyclodehydration of the bromo acid **9**, derived from bromination of **8** in acetic acid, by the Haworth procedure (P_2O_5 in benzene)[5] involved a tedious workup and resulted in a yield of <20% of the hydrindone **10**, so that a



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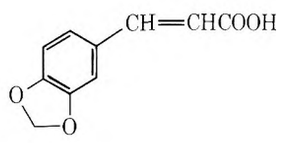

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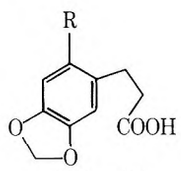
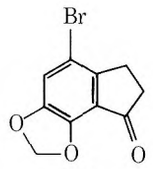


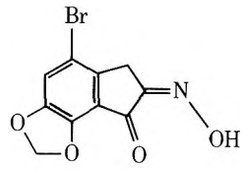
8, R = H
9, R = Br



10

method for achieving this transformation in higher yield was sought. Phosphorus oxychloride, polyphosphoric acid, polyphosphate ester,[6] super polyphosphoric acid,[7] and phosphorus oxychloride/zinc chloride[8] were all tried as cyclizing agents and found to be unsatisfactory. However, when the reaction was run using phosphorus pentoxide in refluxing chlorobenzene under conditions of relatively high dilution, the desired hydrindone **10** was obtained in 40% yield. This material was then nitrosated[9] using isoamylnitrite to afford the α-oximino ketone **11** in 85% yield.

The second-order Beckmann rearrangement of the α-oximino ketone **11** to the bromo diacid **12** had been reported to proceed in 75% yield.[5] However, repeated attempts to duplicate this procedure invariably gave yields on the order of 20%, while the reaction workup was troublesome due to formation of emulsions. Several alternative procedures were investigated, and the best method found involved reaction of **11** in a Schotten–Baumann procedure using *p*-toluenesulfonyl chloride and aqueous sodium hydroxide.[10] The transitory nitrile was immediately hydrolyzed by refluxing the strongly basic reaction mixture until the evolution of ammonia had subsided. Upon acidification, the desired bromo diacid **12** was isolated (51%). Debromination with sodium amalgam then afforded the known 3,4-methylenedioxyhomophthalic acid **13**[5] in 83% yield, or in 8.3% overall yield from piperonal. Fischer esterification of this diacid gave rise to the corresponding diester **14**. The second precursor required for the condensation–cyclization step to the fused lactam was piperonylidenemethylamine (**15**), which was readily prepared



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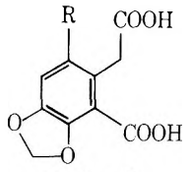
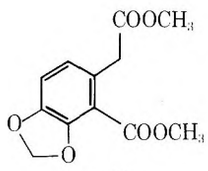
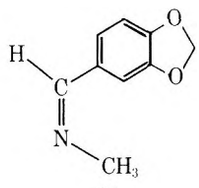


12, R = Br
13, R = H



14

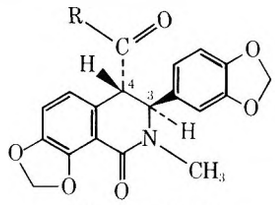


15

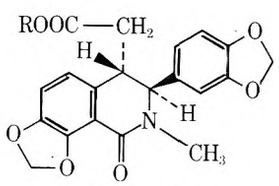
through condensation of piperonal with methylamine.

Condensation of the diester **14** with the Schiff base **15** required refluxing for a week in a sodium methoxide–methanol solution. A requisite added ingredient for this condensation was methylamine gas, which was passed periodically through the mixture. Lactam **16** was thus isolated in 61% yield. The ^1H NMR spectrum of **16** shows the expected signals for two *N*-methyl groups, two methylenedioxys, and five aromatic protons. Present also are two broad peaks at δ 4.17 and 5.42 for the methine protons at C-4 and C-3, respectively. Both of these peaks are resolved into doublets, $J_{3,4}$ = 1 Hz.

Hydrolysis of **16** in 10% aqueous potassium hydroxide afforded the lactam acid **17** in 70% yield. The ^1H NMR spectrum shows only one *N*-methyl signal at δ 3.47, while $J_{3,4}$ = 0 Hz, indicating that the dihedral angle between the hydrogens at C-3 and C-4 must be close to 90°.[11] The corresponding methyl ester **18** exhibits $J_{3,4}$ = 1.5 Hz. Attempts to epimerize the C-4



16, R = $NHCH_3$
17, R = OH
18, R = OCH_3



19, R = CH_3
20, R = H

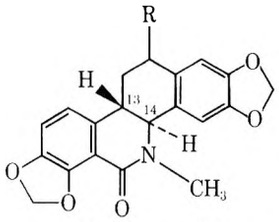
center of **18** with sodium methoxide in methanol gave, as expected, material indistinguishable from **18**, so that the molecule must exist in the thermodynamically more stable trans configuration.

Arndt–Eistert homologation of the lactam acid **17** provided ester **19** (60%), which was saponified to the acid **20**. The C-3 proton in the ^1H NMR spectrum of **20** appears as a broad singlet with no discernible splitting, which corresponds to a 90° angle between the C-3 and C-4 protons, so that these hydrogens also must be trans to each other.[11]

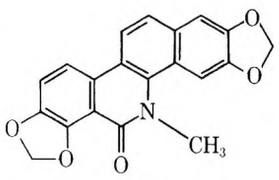
A variety of methods for the cyclodehydration of the acid **20** to the ketone **21** were explored, including phosphorus pentoxide in benzene and in chlorobenzene, polyphosphoric acid by itself and in benzene, super polyphosphoric acid,[7] phosphorus oxychloride, phosphorus oxychloride/zinc chloride,[8] and polyphosphoric ester in chloroform.[6] None of these methods proved satisfactory. The cyclodehydration was then

attempted using a mixture of methanesulfonic acid and phosphorus pentoxide.[12] Under these relatively mild conditions, the desired ketone **21** was generated in 44% yield. The ^1H NMR spectrum of this product shows only four aromatic protons, and the signal for H-14 appears as a doublet, $J_{13,14}$ = 11.5 Hz. This large J value is clearly indicative of a trans diaxial hydrogen relationship.[11]

Sodium borohydride reduction of ketone **21** led to alcohol **22**. Dehydration of this compound using *p*-toluenesulfonic



21, R = =O
22, R = OH



23

acid was accompanied by air oxidation so that oxysanguinarine (**23**) was obtained directly from this step. This material was identical with a sample of oxysanguinarine derived from ferricyanide oxidation of sanguinarine (**3**).[14]

The present synthetic method can be readily adapted to the preparation of such alkaloids as nitidine (**1**) and fagaronine (**2**), since aromatic benzophenanthridine lactams (oxybenzophenanthridenes) are known to be convertible into aromatic benzophenanthridine salts by reduction with lithium aluminum hydride followed by mercuric acetate oxidation.[13]

Experimental Section

Standard Procedures. All melting points were taken on a melting point block and are uncorrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Thin-layer chromatography was on Brinkmann silica gel F-254 plates (0.25-mm thick). Visualization was accomplished by shining UV light on the plates, or by spraying with chromotropic acid reagent. ^1H NMR spectra are in $CDCl_3$ with Me_4Si as internal standard unless specified otherwise.

4-Bromo-6,7-methylenedioxy-1-hydrindone (10). A suspension of 73 g (0.51 mol) of P_2O_5 in 2.1 L of chlorobenzene was refluxed with rapid mechanical stirring. **9**[5] (60 g, 0.22 mol) was added, the mixture turning brown. Refluxing was continued for 2 h. The solution was poured into dilute aqueous NaOH. Workup led to 23 g (40%) of tan prisms: mp 197–199 °C (lit. mp 197–199 °C).[5]

4-Bromo-6,7-methylenedioxy-2-oximino-1-hydrindone (11). To a warm solution of 10 g (39 mmol) of **10** in benzene was added 15 g (0.128 mol) of isoamyl nitrite and 10 mL of concentrated HCl. The mixture was stirred for 2 h at 50 °C. The bright yellow crystals which separated on cooling were collected, washed with methanol, and dried to give 9.48 g (85%) of bright yellow powder: mp 240 °C dec (lit. mp 240 °C dec).[5]

6-Bromo-3,4-methylenedioxyhomophthalic Acid (12). A solution of 14.2 g (0.05 mol) of **11** in 300 mL of cold aqueous NaOH was treated with 55 g (0.26 mol) of *p*-toluenesulfonyl chloride, and the mixture was stirred overnight in a cold water bath. To the resulting black solution, 10 g (0.25 mol) of NaOH was added, and the mixture refluxed 24 h. The cooled reaction mixture was acidifed and extracted with ethyl acetate. The organic extracts were washed with dilute acid, dried, filtered, and evaporated. The dark residue was dissolved in hot methanol, treated with charcoal, and filtered through a Celite pad. The methanol solution was concentrated to 75 mL and 300 mL of hot water was added. Most of the methanol was boiled off. The diacid crystallized upon cooling: 7.73 g (51%); mp 215 °C dec (lit. mp 215 °C dec).[5]

3,4-Methylenedioxyhomophthalic Acid (13). A solution of 6.0 g (20 mmol) of **12** in 200 mL of 1% aqueous NaOH was added to 200 g (0.26 mol of Na metal) of 3% Na/Hg. The temperature was maintained at 90 °C for 16 h. The mixture was filtered, concentrated, and acidified, and the product was collected. The aqueous solution was saturated with NH_4Cl and further extracted with ether. Recrystallization of the combined diacid fractions from hot water gave rise to 3.7 g (83%): mp 201–203 °C (lit. 203–204 °C).[5]

Dimethyl 3,4-Methylenedioxyhomophthalate (14). A solution of 1.0 g (4.4 mmol) of **13** in 50 mL of methanol was saturated with HCl gas and refluxed 16 h. Workup and recrystallization from benzene produced 0.82 g (73%): mp 83–84.5 °C; ν_{max} ($CHCl_3$) 1720 and 1735 cm^{-1}; high-resolution MS calcd for M^+ $C_{12}H_{12}O_6$, *m/e* 252.0623, observed *m/e* 252.0610.

Piperonylidenemethylamine (15). A mixture of 100 g (0.68 mol) of piperonal and 150 g (1.93 mol) of 40% aqueous methylamine was stirred for 3 h and then extracted with ether. The ether solution was dried and evaporated. The residue was placed in a refrigerator where the product crystallized: white needles; 89 g (80%); mp 45–46 °C (lit. mp 46 °C).[15]

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-(*N*-methyl)carboxamide-7,8-methylenedioxy-3,4-dihydroisoquinoline (16).** A sodium methoxide solution was prepared by dissolving 1.5 g (65 mmol) of Na metal in 150 mL of methanol. Addition of 2.5 g (10 mmol) of **14** and 5.2 g (32 mmol) of **15** to this solution gave a pale yellow mixture which was heated to reflux. The mixture was saturated three times a day with methylamine gas, and a mercury seal was used to keep water and air out. Reflux was continued for 7 days, during which time the mixture turned opaque orange, and a yellow solid precipitated.

The solid was filtered off, washed with methanol, and dried. Recrystallization from methanol supplied 2.3 g (61%) of needles: mp 309–311 °C dec; ^1H NMR (TFA) δ 2.93 (3 H, s, NCH_3), 3.37 (3 H, s, NCH_3), 4.17 (1 H, d, $J_{3,4}$ = 1 Hz, H-4), 5.42 (1 H, d, $J_{3,4}$ = 1 Hz, H-3), 5.93 (2 H, s, OCH_2O), 6.22 (2 H, s, OCH_2O), 6.82 (1 H, d, $J_{5,6}$ = 7 Hz, H-6), 7.07 (1 H, d, $J_{5,6}$ = 7 Hz, H-5), and 6.64–6.77 (3 H, m, H-2′, 5′, 6′); ν_{max} (KBr) 1635 and 1655 cm^{-1}; λ_{max} (EtOH) 214 sh, 236 sh, 288, and 321 nm (log ϵ 4.44, 4.17, 3.80, and 3.65).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 63.05; H, 4.94.

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxy-7,8-methylenedioxy-3,4-dihydroisoquinoline (17).** A suspension of 1.4 g (3.66 mmol) of amide **16** in 200 mL of aqueous 10% KOH was refluxed for 48 h under N_2. Workup and recrystallization from methanol supplied 0.95 g (70%): mp 249–254 °C dec; ^1H NMR (TFA) δ 3.47 (3 H, s, NCH_3), 4.25 (1 H, s, H-4), 5.40 (1 H, s, H-3), 5.98 (2 H, s, OCH_2O), 6.27–6.30 (2 H, d, OCH_2O), 6.66–6.95 (3 H, m, H-2′, 5′, 6′), 6.97 (1 H, d, $J_{5,6}$ = 8 Hz, H-6), and 7.17 (1 H, d, $J_{5,6}$ = 8 Hz, H-5).

Anal. Calcd for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09. Found: C, 61.43; H, 4.33.

Methyl Ester of 17. A solution of 0.4 g (1.1 mmol) of **17** in 150 mL of methanolic HCl was refluxed for 12 h. Workup and recrystallization from methanol generated 0.35 g (85%) of ester **18** as prisms: mp 213–214°C; ^1H NMR δ 3.12 (3 H, s, NCH_3), 3.72 (3 H, s, $COOCH_3$), 3.82 (1 H, d, $J_{3,4}$ = 1.5 Hz, H-4), 5.08 (1 H, d, $J_{3,4}$ = 1.5 Hz, H-3), 5.92 (2 H, s, OCH_2O), 6.17 (2 H, s, OCH_2O), 6.60 (1 H, d, $J_{5,6}$ = 7.5 Hz, H-6), 6.83 (1 H, d, $J_{5,6}$ = 7.5 Hz, H-5), and 6.55–6.80 (3 H, m, H-2′, 5′, 6′); ν_{max} (KBr) 1640 and 1730 cm^{-1}; high-resolution MS calcd for M^+ $C_{20}H_{17}NO_7$, *m/e* 383.1004; observed *m/e* 383.1040.

Methyl Ester of *trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxymethyl-7,8-methylenedioxy-3,4-dihydroisoquinoline (19). A solution of 1.18 g (3.20 mmol) of acid **17** in 50 mL of chloroform was treated with 3 mL (35 mmol) of oxalyl chloride and stirred for 18 h in a flask equipped with a $CaCl_2$ drying tube. The solvent was evaporated to dryness, dry benzene was added, and the solvent was again evaporated. The residue was dissolved in chloroform and cooled in an ice bath. This solution was then added slowly to an ethereal diazomethane solution, and the mixture was left standing overnight in an ice bath. The precipitated crystals collected by filtration amounted to 1.05 g (83%) of crude diazoketone. A suspension of this material and 0.5 g of Ag_2O was heated to reflux in 200 mL of methanol for 1 h. The brown mixture was filtered through a Celite pad. The filtrate was evaporated to yield a brown residue. Crystallization from methanol gave 0.76 g (60%) of crystalline ester: mp 199–201 °C; ^1H NMR δ 3.07 (3 H, s, NCH_3), 2.67 (2 H, m, CH_2COOCH_3), 3.68 (3 H, s, OCH_3), 3.35 (1 H, m, H-4), 4.52 (1 H, d, $J_{3,4}$ = 1 Hz, H-3), 5.82 (2 H, s, OCH_2O), 6.05 (2 H, s, OCH_2O), and 6.32–6.77 (5 H, m, ArH); ν_{max} (KBr) 1643 and 1720 cm^{-1}; λ_{max} (EtOH) 215 sh, 235 sh, 286, and 320 nm (log ϵ 4.44, 4.20, 3.77, and 3.64); high-resolution MS calcd for M^+ $C_{21}H_{19}NO_7$, *m/e* 397.1160; observed *m/e* 397.1159.

***trans*-1-Oxo-2-methyl-3-(3′,4′-methylenedioxy)phenyl-4-carboxymethyl-7,8-methylenedioxy-3,4-dihydroisoquinoline (20).** A suspension of 750 mg (1.89 mmol) of **19** in 100 mL of 10% aqueous KOH was refluxed for 3 h and the hot brown solution was treated with decolorizing carbon, filtered through a Celite pad, acidified with concentrated HCl, and extracted with chloroform. The extracts were washed with water and dried and the solvent was evaporated. The

residue was recrystallized from methanol: 615 mg (85%) of prisms; mp 244–246 °C dec; ^{1}H NMR (TFA) δ 3.40 (3 H, s, NCH_3), 2.95 (2 H, dd, CH_2COOH), 3.75 (1 H, m, H-4), 4.95 (1 H, br s, H-3), 5.87 (2 H, s, OCH_2O), 6.17 (2 H, s, OCH_2O), and 6.55–7.08 (5 H, m, ArH); ν_{max} (KBr) 1613, 1715, and 2400–3200 cm^{-1}.

Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.65; H, 4.47. Found: C, 62.72; H, 4.40.

***trans*-5,8-Dioxohexahydrosanguinarine (21).** A solution of 5 g (35 mmol) of P_2O_5 in 50 g of methanesulfonic acid was warmed to 45 °C. To this solution was added 500 mg (1.31 mmol) of the above acid **20**, and the mixture was stirred for 2 h while the temperature was maintained at 45 °C. The mixture was poured into ice water and extracted with chloroform. The organic solution was extracted with dilute aqueous NaOH and with water and dried, and the solvent was evaporated. The residue crystallized from ethanol: 210 mg (44%) as tan prisms; mp 277–280 °C dec; ^{1}H NMR (TFA) δ 3.38 (3 H, s, NCH_3), 2.55–4.08 (3 H, m, H-6 and H-13), 5.28 (1 H, d, $J_{13,14}$ = 11.5 Hz, H-14), 5.33 (2 H, s, OCH_2O), 5.38 (2 H, s, OCH_2O), 6.85 (1 H, d, $J_{11,12}$ = 8 Hz, H-12), 7.02 (1 H, s, H-1), 7.15 (1 H, d, $J_{11,12}$ = 8 Hz, H-11), 7.53 (1 H, s, H-4); ν_{max} ($CHCl_3$) 1640 and 1675 cm^{-1}; λ_{max} (EtOH) 213, 237, 273, and 317 nm (log ϵ 4.48, 4.60, 4.02, and 4.07).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14. Found: C, 65.71; H, 4.01.

5-Hydroxy-8-oxohexahydrosanguinarine (22). A suspension of 100 mg (0.27 mmol) of the above keto lactam **21** and 100 mg (13 mmol) of $NaBH_4$ in 100 mL of isopropyl alcohol was stirred at room temperature for 16 h. The solvent was evaporated and water added to the residue. The mixture was acidified with councentrated HCl and extracted with chloroform. The organic extracts were washed with water and dried and the solvent was evaporated. The residue crystallized from methanol: 75 mg (74%) of white prisms; mp 281–283 °C dec; ν_{max} (KBr) 1620 and 3150–3600 cm^{-1}; λ_{max} (EtOH) 219 sh, 236 sh, 290, and 318 nm (log ϵ 4.40, 4.17, 3.80, and 3.59).

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66. Found: C, 65.20; H, 4.76.

Oxysanguinarine (23). A solution of 50 mg (0.14 mmol) of lactam alcohol **22** and 10 mg of *p*-toluenesulfonic acid in 50 mL of benzene was refluxed for 16 h. The solvent was evaporated and the residue was dissolved in chloroform. The solution was extracted with 5% aqueous $NaHCO_3$ and dried, and the solvent was evaporated. The residue was subjected to preparative TLC using a 3:97 methanol–chloroform solvent system. A compound with an R_f 0.62, which was significantly higher than the R_f (0.29) of the starting lactam alcohol, was obtained. Recrystallization from ether gave 15 mg (30%), mp 347–349 °C dec, spectrally and chromatographically identical with oxysanguinarine: ν_{max} ($CHCl_3$) 1645 cm^{-1}; λ_{max} (EtOH) 241, 281 sh, 289, 331, 348, 370, and 385 nm (log ϵ 4.27, 4.61, 4.70, 4.17, 4.18, 4.06, and 4.02).

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Registry No.—**9,** 56920-74-2; **10,** 38699-84-2; **11,** 66271-19-0; **12,** 66271-20-3; **13,** 66303-84-2; **14,** 66271-21-4; **15,** 63254-33-1; **16,** 66271-22-5; **17,** 66271-23-6; **18,** 66303-85-3; **19,** 66271-24-7; **20,** 66271-25-8; **21,** 66271-26-9; **22,** 66271-27-0; **23,** 548-30-1; piperonal, 120-57-0; methylamine, 74-89-5.

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Chemistry of Chelocardin. 3.[1] Structure and Synthesis of Isochelocardin

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Isochelocardin (**2**), a minor component of the chelocardin fermentation, was shown to be a condensation product of two molecules of chelocardin. Carbobenzoxyisochelocardin acethydrazone (**9**) was synthesized by treatment of carbobenzoxychelocardin with chelocardin acethydrazone, thus confirming the assigned structure. The synthesis of isochelocardin itself is also described.

During the isolation of chelocardin (**1**),[2,3] a potent broad-spectrum antibiotic produced by *Nocardia sulphurea* (NRRL-2822), a contaminant which we designated as isochelocardin, was noted to be present and was subsequently isolated as a hydrochloride salt after chromatographic separation. This compound was present in the isolated chelocardin in proportions ranging from 1 to 3%. In view of the potential

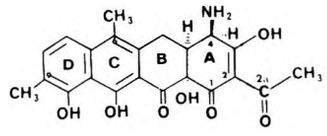

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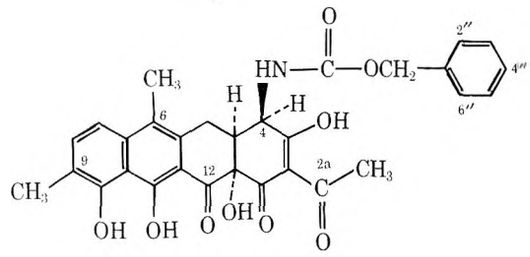
Table I. Comparative ^{13}C NMR Chemical Shift data[a] of Carbobenzoxy-β-chelocardin (4) and Carbobenzoxyisochelocardin



4

Region	4	Assignment[c]	Carbobenzoxy-isochelocardin	Region	4	Assignment[c]	Carbobenzoxy-isochelocardin
Carbonyl	200.8	12	202.7, 200.3	Aromatic	121.9	6	121.7
	200.5	2a	199.6, 199.0		119.0	9	119.3, 118.9
	196.0	1	192.5, 191.8		114.3	7	114.4, 114.3
	190.7	3	191.7, 191.3		111.2	2, 11a	111.4, 110.8
			175.1, 174.3		108.7	10a	109.0, 108.8, 108.7, 107.3, 106.8
Aromatic	162.5	11	162.9, 162.6, 162.1	Aliphatic	79.0	12a	79.8, 77.8
	157.0	C(O)N	156.7		66.1	$-CH_2Ph$	65.6
	154.7	10	154.7, 154.6		53.1	4	56.7, 55.1
	136.9	6a	136.9		41.7	4a	*b*
	136.8	1″	135.2		26.3	2a-CH_3	27.1
	135.0	8	134.9		25.6	5	26.5
	129.7	5a	130.4, 129.6, 129.3				18.1, 17.8
	128.4	2″, 6″	128.3		15.2	9-CH_3	15.2
	128.0	3″, 4″, 5″	127.8		13.7	6-CH_3	13.7

[a] Chemical shift data are given in ppm downfield from internal Me_4Si and spectra taken in Me_2SO. [b] Resonances in the aliphatic region in the carbobenzoxyisochelocardin spectrum at ~40 ppm were obscured by solvent peaks. [c] Assignments for compound **4** are taken from ref 7.

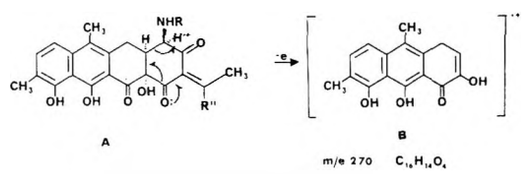
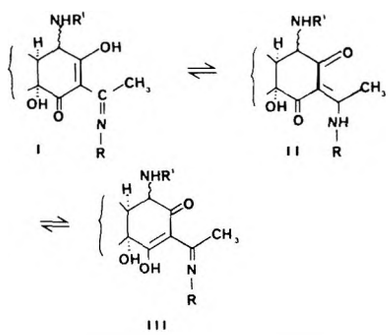


Figure 1. Major fragmentation of chelocardin and analogues.

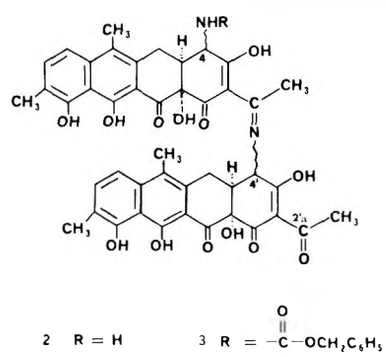
clinical use of chelocardin, the characterization of isochelocardin was of particular interest. Isochelocardin is somewhat unstable in solution at room temperature, giving rise to new impurities at a rate which depends on the nature of the solvent.

The UV absorption spectrum of isochelocardin, whose structure is shown in this report to be **2**,[8] has the characteristic chelocardin peaks[4] λ_{max}^{MeOH} 226 (ε 36 000), 273 (ε 50 400), and 438 nm (ε 9 600) and an additional absorption at 307 nm (ε 20 500). It had been observed[5] in this laboratory that 2a-substituted chelocardin analogues (in which the 2a-carbonyl group is replaced by an imine) normally possess an additional absorption at 307–312 nm. The presence of this additional absorption (307 nm) in isochelocardin suggested the possibility that it has a chelocardin skeleton with an imino substituent at the C_{2a} position.

The IR spectrum of isochelocardin shows significant difference to that of chelocardin[6] in the carbonyl region (1600–1700 cm^{-1}), but little information could be obtained from it other than an indication of the presence of a β-hydroxy-α,β-unsaturated carbonyl function or alternatively a β-amino-α,β-unsaturated carbonyl function. The ^1H NMR spectrum of this compound was of very poor resolution.[9]

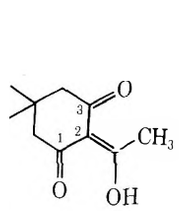


Isochelocardin formed a carbobenzoxy derivative **3** (mp 238–243 °C) upon treatment with benzyl chloroformate. The IR spectrum of **3** showed a carbamate absorption at 1730 cm^{-1}, and its ^1H NMR spectrum was poorly resolved. *N*-Carbobenzoxyisochelocardin showed a similar UV spectrum to that of the starting isochelocardin. The mass spectrum of **3** showed no molecular ion but the presence of several frag-



2 R = H 3 R = $-\overset{O}{\overset{\|}{C}}-OCH_2C_6H_5$

Table II. Some Comparative ^{13}C NMR Chemical Shift Data[a] of Carbobenzoxy-β-chelocardin and Its Analogues and 2-Substituted Dimedones



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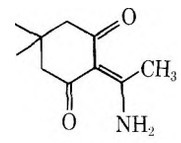

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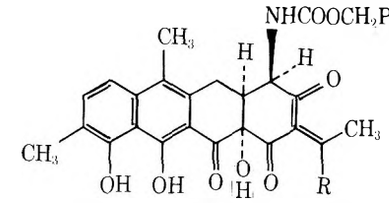


4 (R = OH), 7 (R = NH_2), 8 (R = $NHCH_2Ph$)

Assignments[c]	5	6	4	7	8
C_1	196.3	196.5	196.0	192.0	192.2
C_3	196.3	196.5	190.7	190.8	191.3
C_2	112.0	106.5	111.2	105.0	106.4
C_{2a}[b]	201.6	173.2	200.5	174.7	173.8
$C_{2a}CH_3$[b]	28	24	26.3	23.8	17.8

[a] Chemical shift data are given in ppm downfield from internal Me_4Si and spectra taken in Me_2SO. [b] Substantial upfield shift by substitution at C_{2a} carbonyl. [c] Assignments were taken from ref 7.

ments normally found in the mass spectra of chelocardin analogues; the most important and prominent ion can be assigned to structure B shown in Figure 1 (*m/e* 270, $C_{16}H_{14}O_6$)[4] confirming our previous observation that isochelocardin contains the basic chelocardin skeleton.

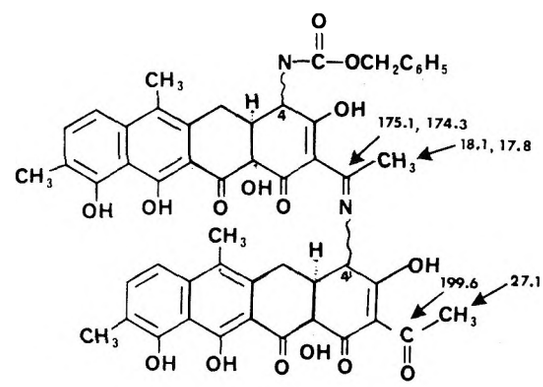
Carbobenzoxyisochelocardin (**3**) was subjected to detailed ^{13}C NMR analysis. The chemical shift data along with those of carbobenzoxychelocardin (**4**)[7] are presented in Table I. The remarkable feature of the ^{13}C NMR spectrum of compound **3** is that in many cases there are two or more resonances for each carbon of compound **4**. This suggested that carbobenzoxyisochelocardin was a mixture of two isomers in approximately equal proportions and/or that its molecular structure incorporated two molecules of chelocardin.

The ^{13}C NMR chemcal shifts[7] of the three carbonyl carbons of the β-triketone system and also the 2a-methyl of chelocardin are profoundly affected by substitution on the 2a-carbonyl, as illustrated in Table II. In each case, the C_{2a} and C_{2a}-methyl carbon resonances undergo substantial upfield shifts.

These changes are extremely useful in the structural determination of isochelocardin. In addition to our previous observation from UV and ^{13}C NMR spectra, the presence of resonance at 175.1 and 174.3 as well as at 18.1 and 17.8 ppm together with resonances at 199.6, 199.0, and 27.1 ppm in the ^{13}C NMR spectrum of carbobenzoxyisochelocardin (see Figure 2) suggested that isochelocardin has a "dimeric" structure formed by a Schiff base condensation of two molecules of chelocardin with the loss of a molecule of water. Carbobenzoxyisochelocardin would then be represented by **3**, a structure consistent with its elemental analysis. The presence of signals in its mass spectrum at *m/e* 503 and 435 is also consistent with structure **3** in that they can arise from fragmentation as outlined in Figure 3.

To confirm that carbobenzoxyisochelocardin was indeed **3** and not just a mixture of two isomers of a mono-2′-substituted carbobenzoxychelocardin, carbobenzoxyisochelocardin was converted to its acethydrazone **9** by reaction with acethydrazide in tetrahydrofuran (Scheme I), by analogy to the preparation of hydrazones from chelocardin and carbobenzoxy-chelocardin.[5] The formation of compound **9** established the presence of a free β-tricarbonyl system in the A ring of carbobenzoxyisochelocardin. The ^{13}C NMR (see Table III) and UV data for **9** are consistent with hydrazone substitution in the 2a position of a chelocardin moiety.

The structure of carbobenzoxyisochelocardin acethydrazone (**9**) was confirmed by synthesis. Treatment of carbobenzoxychelocardin with chelocardin acethydrazone hydrochloride (**10**)[5] in dimethylformamide in the presence of sodium bicarbonate gave, after purification, a clean product having the same R_f as compound **9** on TLC analysis. This product was made by reacting two distinct compounds in more than 70% yield with gradual disappearance of both starting materials; it is therefore unlikely that it was a rearrangement product of either one of the starting materials, as in that case



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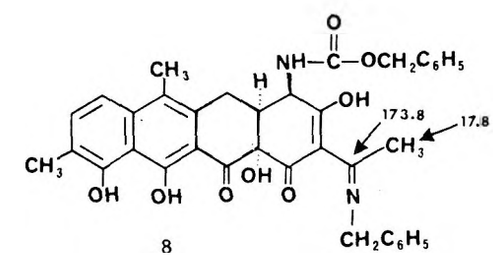

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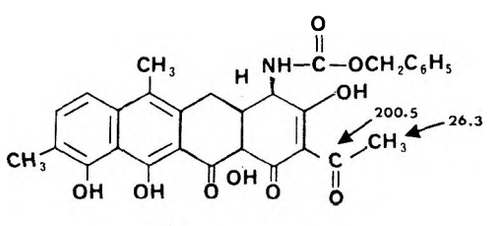

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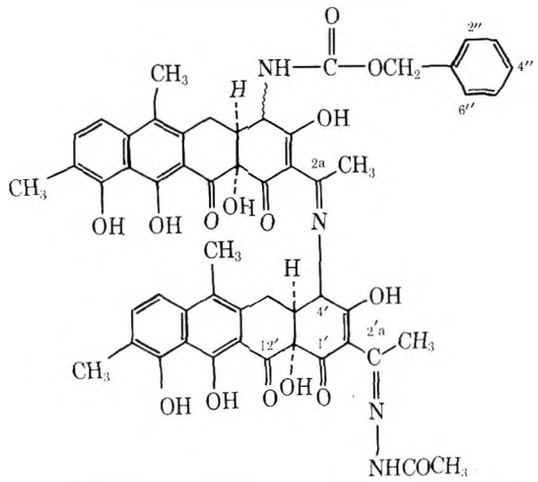
Figure 2. Some important ^{13}C NMR chemical shifts (in ppm downfield from internal Me_4Si) of carbobenzoxychelocardin derivatives as taken from ref 6.

Table III. Comparative ^{13}C NMR Chemical Shift Data[a-c] of Carbobenzoxyisochelocardin Acethydrazone (9) and Its Synthetic Counterpart (11)



11	9	Assignment	11	9	Assignment	11	9	Assignment
202.3	202.2	12, 12′	136.8	136.8	6a	107.2	107.2	2
200.7	200.0		134.8 × 2	134.7 × 2	8, 8′	104.2	104.2	2′
192.6	193.1*	1, 1′	130.4	130.4	5a, 5′a	79.7	79.7	12a
191.2	191.2		129.0	129.1	4″	78.8*	78.8*	($CHCl_3$ trace)
189.7	189.8	3, 3′	128.3 × 2	128.3 × 2	2″, 6″	78.5	78.4	12′a
188.7	188.7		127.8 × 2	127.8 × 2	3″, 5″	65.7	65.7	-CH_2Ph
174.9	174.9	2a	121.4	121.3*	6, 6′	57.5*	57.6*	4, 4′
169.3	169.3	2′a	121.2	121.2		54.9*	54.9*	
167.1	167.2	NHC(O)CH_3	118.9	118.7 × 2	9, 9′	25.8*	25.8*	5, 5′
162.8	163.2*	11, 11′	118.7			25.1*	24.8*	
162.3	162.7		114.2 × 2	114.2 × 2	7, 7′	20.2	20.2	2′a-CH_3
157.0	157.0	NHC(O)O	111.4	111.6	11a, 11′a	18.4	18.4	2a-CH_3
	155.2	10, 10′		111.5		18.3*	16.9	-NH-C(O)CH_3
154.7	154.8		108.9	108.9	10a, 10′a	16.9	15.1 × 2	9-CH_3, 9′-CH_3
136.9 × 2	136.9 × 2	1″, 6′a	108.6	108.6		15.1 × 2	13.6 × 2	6-CH_3, 6′-CH_3
						13.6 × 2		

[a] Chemical shift data are given in ppm downfield from internal Me_4Si and spectra taken in Me_2SO. [b] Shifts marked * were not generated by the computer but were hand calculated and are less precise; those marked ×2 are of double intensity, although in some cases the peaks are not twice as tall but reather broadened. [c] Resonances in aliphatic regions around 40 ppm were obscured by solvent.

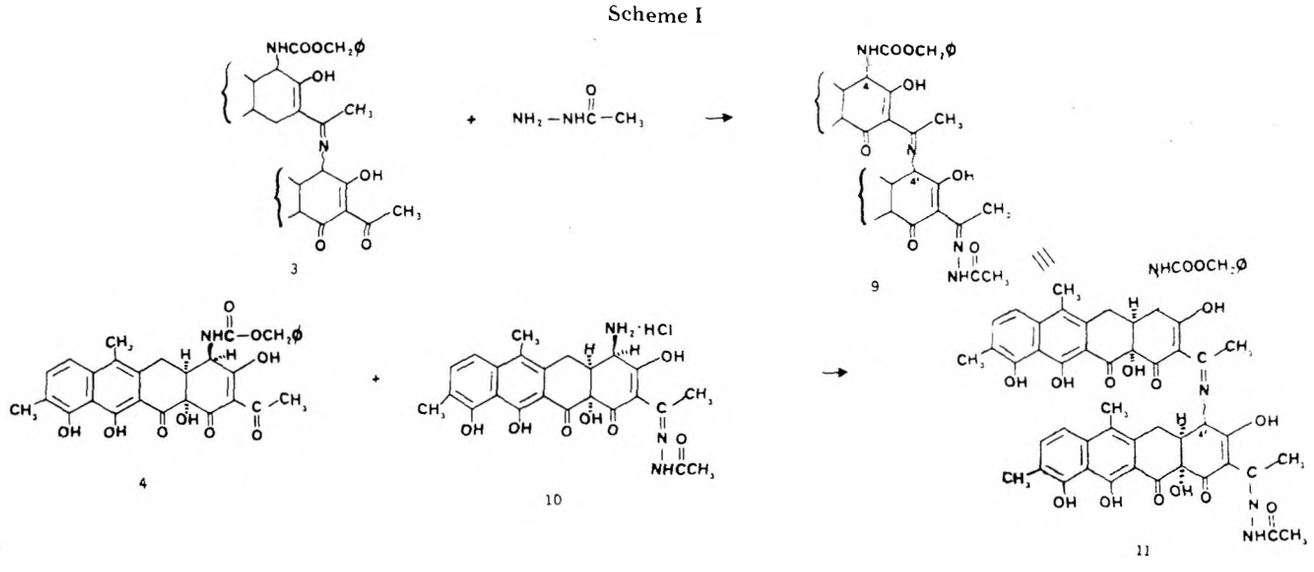
one would expect to have no more than 50% conversion. Furthermore, neither of the starting materials alone gave the product under the same experimental conditions.

The product must therefore be the expected condensation product, the Schiff base **11**. Its elemental analysis showed a nitrogen value which is compatible with a "dimeric" structure and its structure was further confirmed by ^{13}C NMR analysis (Table III).

Compound **11** appeared as one spot on TLC and appeared to be identical to compound **9**, having the same R_f in TLC, identical elemental analysis, ^{13}C NMR, and UV spectra, and *very similar IR spectra. Thus, compounds 9 and 11 are* unambiguously identical.

Under the same experimental conditions used to prepare compound **11**, a considerable amount of chelocardin acethydrazone (**10**) epimerized to its α epimer at C_4 (**12**). Hence,

Scheme I



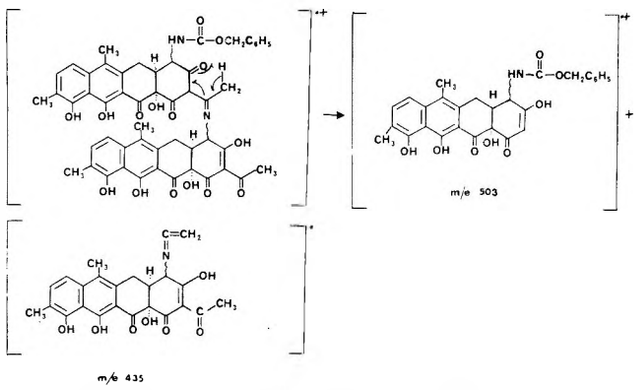
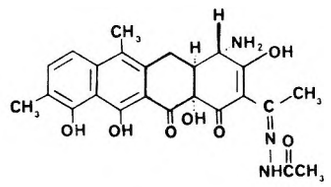


Figure 3. Initial fragmentation of carbobenzoxyisochelocardin **3**.

compound **11** as well as **9** should be a mixture of components isomeric at $C_{4'}$. This possibility was confirmed by LC. LC analysis indicated that compound **11** was a mixture of two components in a ratio of 2:1. Compound **9** has the same re-



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tention volumes as compound **11** (the ratio of the two components was 95:5). (The presence of additional isomers differing at the C_4 atom cannot be excluded, since it is possible that the LC conditions we employed did not resolve the epimer at C_4.)

Since the structure of carbobenzoxyisochelocardin acethydrazone (**11**) is confirmed, the structure of isochelocardin is fully established to be **2**, having a mixture of at least two epimers presumably at $C_{4'}$.

Isochelocardin (**2**) was synthesized by reacting chelocardin hydrochloride with a 1 molar equiv of chelocardin free base in THF to give a 65% conversion to a mixture of products with a major component having the same R_f in three different TLC systems and identical retention volumes in LC analysis as isochelocardin.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were recorded on a Beckman Model IR8 infrared spectrophotometer. The ^{1}H NMR spectra were recorded on Varian Associates EM-360 and HA-100 spectrometers in deuterated solvents; resonance positions are given on the δ scale (ppm) relative to internal tetramethylsilane. The mass spectra were recorded on an AEI MS-902 double-focussing mass spectrometer. The UV spectra were recorded on a Unicam SP-800A spectrometer in 0.1 N methanolic hydrogen chloride solution. The ^{13}C NMR spectra were recorded on a Varian Associates XL-100-15/TT-100 spectrometer system in Me_2SO; resonance positions are give in ppm relative to internal tetramethylsilane. Parameters used were pulse width (30°) 3.5 μs, pulse delay 0.5–1.0 s, 6K sweep width, and 8K data table. LC analyses were performed on a Waters Associates ALC-202 instrument through a phenyl/corasil column ($\frac{1}{8}$ in. × 24 in.). Detection was by UV absorbance at 280 nm. Injections were performed with a Waters Model U6K injector.

The IR absorption spectrum of isochelocardin hydrochloride is uncharacteristic. Since the various derivatives reported here have a β-hydroxy-α,β-unsaturated carbonyl function which would have a similar absorption to the β-diketone system, very little change in the carbonyl absorption region (1580–1680 cm^{-1}) was observed. However, the changes in relative intensity of the carbonyl absorptions correlated with the structural changes. Thus, only the relevant difference in absorption bands will be mentioned in the Experimental Section. Since all the ^{1}H NMR spectra obtained are of poor resolution, they are not reported. The relevant ^{13}C NMR data are given above.

The abbreviations used both in the text and in the Experimental Section are designated as follow: TLC, thin layer chromatography; DMF, dimethylformamide; THF, tetrahydrofuran; IR, infrared; UV, ultraviolet; ^{1}H NMR, proton magnetic resonance; ^{13}C NMR, carbon magnetic resonance; LC high pressure liquid chromatography.

Isolation of Isochelocardin Hydrochloride (2). Crude chelocardin–calcium chloride complex from fermentation sources having 2% of isochelocardin was chromatographed on Sephadex (LH-20) using a 0.1 N methanolic hydrogen chloride solution as the eluting solvent. The isochelocardin hydrochloride was isolated as a deep orange amorphous solid: UV λ_{max}^{MeOH} 226 (ϵ 36 000), 273 (ϵ 50 400), 307 (ϵ 20 500), and 438 nm (ϵ 9 600).

Carbobenzoxyisochelocardin (3). Sodium bicarbonate (168 mg; 2 mM) and benzyl chloroformate (120 mg; 0.67 mM) were added to a solution of isochelocardin **2** (200 mg; 0.45 mM) in 50 mL of 96% aqueous THF. The reaction mixture was stirred for 1 h at room temperature. Water (45 mL) was added and the THF was evaporated under reduced pressure. The aqueous suspension was extracted with ether. After decanting the ether, the aqueous layer was acidified to pH 1–2 with 5% hydrochloric acid and extracted with chloroform (2 × 80 mL). The chloroform extract was washed twice with water, dried, and evaporated to dryness. The residue was washed with ether to give 192 mg of product **3**: mp 238–243 °C; UV λ_{max}^{MeOH} 224 (ϵ 50 000), 273 (ϵ 77 000), 300 (ϵ 33 000), 311 (ϵ 30 000), and 432 nm (ϵ 11 000); the IR spectrum showed a carbamate absorption at 1730 cm^{-1}; MS *m/e* 503, 435, 394, 270, 255, 109, and 91. Anal. Calcd for $C_{52}H_{46}N_2O_{15}$: C, 66.50; H, 4.90; N, 2.99; O, 25.60. Found: C, 66.73; H, 5.09; N, 2.91; O, 25.25.

Carbobenzoxyisochelocardin Acethydrazone (9). Acethydrazone (24.5 mg; 0.33 mM) was added to a solution of carbobenzoxyisochelocardin (**3**) (180 mg; 0.33 mM) in 25 mL of THF and the mixture was stirred at room temperature for 1 h. The solution was then evaporated to dryness under reduced pressure, taken up in chloroform (3 mL), and precipitated with methanol. Upon filtration, a dark yellow solid was obtained, which was then purified by preparative thin layer chromatography on Quanta-gram precoated silica plates (eluting solvent system: chloroform–methanol–acetic acid (20:1:1 v/v aged for 24 h)), yielding compound **9** (145 mg): UV λ_{max}^{MeOH} 224 (ϵ 49 000), 272 (ϵ 80 000), 300 (ϵ 43 300), 311 (ϵ 43 300), and 430 nm (ϵ 11 900). Anal. Calcd for $C_{54}H_{50}N_4O_{15}$: C, 64.18; H, 5.06; N, 5.63; O, 24.12. Found: C, 64.50; H, 5.00; N, 5.37; O, 24.90.

Condensation between Carbobenzoxychelocardin and Chelocardin Acethydrazone (Synthetic Carbobenzoxyisochelocardin Acethydrazone (11)). Carbobenzoxychelocardin[6] (545 mg; 1 mM) and chelocardin acethydrazone hydrochloride[5] (502 mg; 1 mM) were dissolved in 12 mL of DMF. Sodium bicarbonate (84 mg; 1 mM) was added and the mixture was stirred for 5 days at room temperature. It was then added dropwise to 500 mL of ether and filtered. After purification by preparative thin layer chromatography on Quantagram Q. silica precoated plates (eluting solvent system: chloroform–methanol–acetic acid (20:1:1)) a 730 mg (72%) yield of **11** was obtained: UV λ_{max}^{MeOH} 224 (ϵ 51 000), 272 (ϵ 84 000), 300 (ϵ 45 000), 311 (ϵ 45 000), and 430 nm (ϵ 12 000). Anal. Calcd for $C_{54}H_{50}N_4O_{15}$: C, 64.18; H, 5.06; N, 5.63; O, 24.12. Found: C, 65.00; H, 5.20; N, 5.55; O, 24.80.

LC Determinations of Compounds 9 and 11. With a flow rate of 2 mL/min and using a step change procedure, starting with a mixture containing 17.50% (v/v) of acetonitrile in a 0.01 M Na_2ETDA aqueous solution adjusted to pH 8.8 and changing 5 min after injection to a mixture containing 17.43% (v/v) of acetonitrile, compound **9** was shown to have two components in the ratio of 5:95 with retention volumes of 22 and 30 mL, respectively. Under identical conditions, compound **11** was also shown to be a mixture of two components in the ratio of 1:2 with retention volumes of 22 and 30 mL, respectively.

Preparation of Isochelocardin (by Synthesis). Chelocardin hydrochloride (223 mg; 0.5 mM) was added to a solution of chelocardin free base (205 mg; 0.5 mM) in tetrahydrofuran. After stirring for a period of 15 h, a mixture of several compounds was observed. The major component had a R_f identical to isochelocardin (**2**) in three different TLC systems: (1) Quanta-gram silica gel plates deactivated with 10% oxalic acid in methanol and developed with chloroform–methanol–formic acid (90:10:5); (2) Merck aluminum precoated silica gel plates oxalic acid deactivated and developed with chloroform–methanol–formic acid (80:20:5); and (3) Merck aluminum precoated polyamide **11** plates developed with Chloroform–methanol–formic acid (90:10:5). After performing a gel filtration through Sephadex LH-20, the mixture was subjected to LC analysis using 10% acetoni-

trile in 0.01 M Na_2ETDA solvent at pH 7.8 (flow rate 2 mL/min) and the major component was found to be identical to isochelocardin according to retention volume (26 mL). The major component could not be isolated in pure enough form for full characterization.

Acknowledgment. We thank G. Nettleship for recording ^1H NMR spectra and LC analyses, Sandra L. Mueller and Ruth S. Stanaszek of Abbott Laboratories, North Chicago, for recording the mass spectra and ^{13}C NMR spectra, respectively, and the staff of the microanalytical department of Abbott Laboratories for the elemental analyses.

Registry No.—**1**, 29144-42-1; **1** HCl, 56433-46-6; **2**, 66290-79-7; **2** HCl, 66290-80-0; **3**, 66290-81-1; **4**, 65805-84-7; **9**, 66290-82-2; **10**, 66290-83-3; acethydrazone, 1068-57-1.

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(6) D. T. W. Chu, D. L. Garmaise, and E. Bernstein, *Can. J. Chem.*, **53**, 1434 (1975).
(7) R. S. Egan, R. S. Stanaszek, E. Bernstein, D. T. W. Chu, and S. N. Huckin, manuscript in preparation.
(8) In this paper structures are given as tautomer (I) for simplicity but an equilibrium with the other tautomeric forms II and III is not excluded.
(9) It has been observed[4] that the ^1H NMR spectra of chelocardin and its derivatives (other than 4-*N*-acyl derivatives) are poorly resolved.

Synthesis and Mass Spectrometry of Some Structurally Related Nicotinoids

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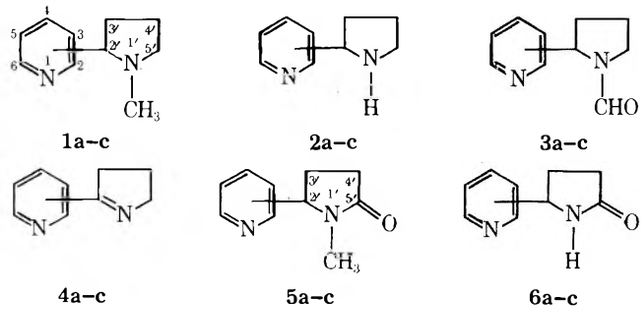
The synthesis and mass spectrometry of a group of structurally related nicotinoids (**1a–c–6a–c**) have been investigated. A detailed discussion is presented of their complex electron-induced fragmentation mechanisms, established with the aid of 27 site-labeled deuterium analogues, high-resolution measurements, and metastable ion studies.

Substantial interest in the minor tobacco alkaloids, their mammalian metabolites, and the physiological effects of nicotine has been noted in the recent literature.[2–4] Further, the widespread occurrence of nicotine-like compounds in nature,[5,6] as well as the expanding interest in the trace components of tobacco and tobacco smoke,[7] have led us to undertake an investigation of the preparation and spectral properties of a group of structurally related nicotinoids (**1a–c–6a–c**). The



1a–c **2a–c** **3a–c**

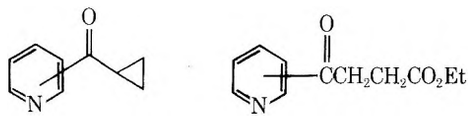
4a–c **5a–c** **6a–c**

a = 2-pyridyl; b = 3-pyridyl; c = 4-pyridyl

results of our synthetic and mass spectrometric studies are reported here.

Synthesis.[8] Despite the extensive studies[2–6,9–11] reported on the *Nicotiana* alkaloids (**1b–4b**), their metabolites (**5b** and **6b**), and a host of analogues, only a limited amount of diffuse work has been carried out on the isomeric nicotinoids (**1a,c–6a,c**).[12] It therefore seemed appropriate to investigate the applicability of newer methods of alkaloid synthesis to the preparation of this cohesive group of structurally related, isomeric nicotinoids.

The reaction of cyclopropyl 3-pyridyl ketone (**7b**) with formamide has been shown to give 3-nornicotine[13] (**2b**; via acid



7a–c **8a–c**

a = 2-pyridyl; b = 3-pyridyl; c = 4-pyridyl

hydrolysis of *N'*-formyl-3-nornicotine (**3b**), generated in situ). This method was chosen as a route to the nornicotines (**2a** and **2c**) and the *N'*-formylnornicotines (**3a–c**). After having first established that **3b** could be isolated from the reaction of **7b** with formamide, the synthesis was used to prepare 2- and 4-nornicotine (**2a** and **2c**) and *N'*-formyl-2- and *N'*-formyl-4-nornicotine (**3a** and **3c**) from the appropriate cyclopropyl pyridyl ketone (**7a,c**).

The cotinines (**5a** and **5c**) were prepared by treatment of the pyridoylpropionates (**8a** and **8c**) with *N*-methylformamide using an altered version of Sugasawa's method.[14] The prerequisite α-keto esters were obtained from the reaction of ethyl acrylate with 2- and 4-pyridinecarboxaldehyde,[15] a method which was found preferable to the published procedure.[16]

Attempts to apply the cotinine synthesis to the preparation of the norcotinines (**6a** and **6c**) by substituting formamide for *N*-methylformamide were unsuccessful. However, **6a** and **6c** could be obtained by reaction of the appropriate α-keto ester (**8a** or **8c**) with NH_4Cl and $NaBH_3CN$.

During the course of our study, Hu[18] reported an excellent improvement of Späth's original 3-myosmine (**4b**) synthesis.[19] This method,[18] with some modification, was used to prepare the myosmines (**4a–c**).

The synthesis of the deuterated nicotinoids (Table I), necessary for both this and NMR studies,[20] proved facile ex-

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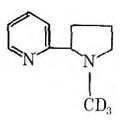
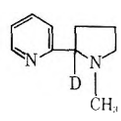
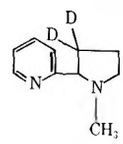
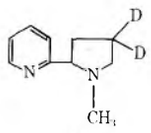
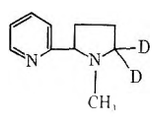
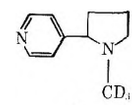
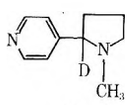
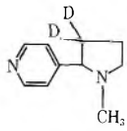
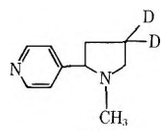
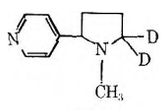
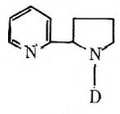
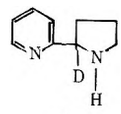
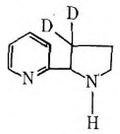
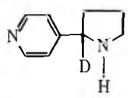
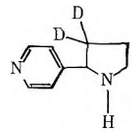
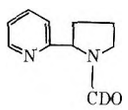
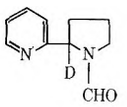
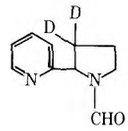
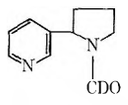
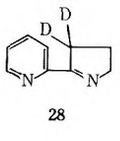
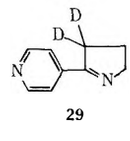
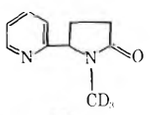
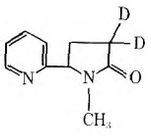
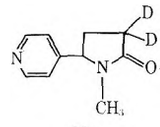
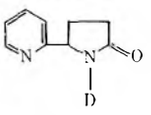
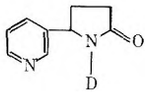
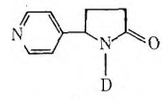
Table I. Deuterated Analogues

Compd[a]	Isotopic purity[b]	Compd[a]	Isotopic purity[b]	Compd[a]	Isotopic purity[b]
 9	97% d_3	 10	90% d_1	 11	87% d_2 12% d_1
 12	94% d_2 5% d_1	 13	95% d_2 5% d_1	 14	90% d_3
 15	86% d_1	 16	89% d_2 10% d_1	 17	85% d_2 12% d_1
 18	95% d_2 5% d_1	 19	97% d_1	 20	91% d_1
 21	88% d_2 9% d_1	 22	89% d_1	 23	88% d_2 10% d_1
 24	90% d_1	 25	93% d_1	 26	83% d_2 14% d_1
 27	84% d_1	 28	89% d_2 10% d_1	 29	88% d_2 11% d_1
 30	98% d_3	 31	97% d_2 2% d_1	 32	81% d_2 17% d_1
 33	92% d_1	 34	94% d_1	 35	95% d_1

[a] The structure and site of labeling were validated by comparison of their ^{1}H NMR and mass spectra with those of authentic nondeuterated compounds. The site of labeling was further confirmed by ^{2}H NMR spectroscopy (**9**–**18** and **20**–**32**). [b] Determined by mass spectral analysis (**9**–**35**) and confirmed by ^{1}H NMR spectroscopy (**9**–**18** and **20**–**32**).

cept in a few cases. The 2-cotinine-*4′,4′*-d_2 (**31**) was synthesized by deuterium exchange of the 4′ protons of **5a** by an established procedure.[21] This method (D_2O and K_2CO_3 at 101 °C for 12 days) could not be used to synthesize 4-cotinine-*4′,4′*-d_2 (**32** from **5c**) because it also caused exchange of the 2′ proton, giving 4-cotinine-*2′,4′,4′*-d_3 (45.6% d_3, 50.3% d_2, and 3.2% d_2).[22] If the K_2CO_3 was replaced by $KHCO_3$ and the reaction time shortened, **32** was obtained. The 2-cotinine-*methyl*-d_3 (**30**) was prepared from **8a** and CD_3NH_2·HCl via the method developed for the synthesis of the norcotinines. Reduction of the myosmines (**4a** and **4c**) with $NaBD_4$ yielded 2- and 4-nornicotine-*2′*-d_1 (**20** and **22**). Sodium borohydride reduction of 2- and 4-myosmine-*3′,3′*-d_2 (**28** and **29**, obtained from **4a** and **4c** by acid-catalyzed exchange of the 3′ protons) gave 2- and 4-nornicotine-*3′,3′*-d_2 (**21** and **23**). The 4-nicotine-*2′*-d_1 (**15**) was synthesized by iodomethylation of **22** because the methylation of **22** under Clark–Eschweiler conditions[13] resulted in loss (ca. 90%) of the deuteron. Formylation of **21** with HCO_2H and **2b** with DCO_2D afforded the *N′*-formyl derivatives **26** and **27**. This method could not be used to prepare *N′*-formyl-d_1-2-nornicotine (**24**) from **2a** or *N′*-formyl-2-nornicotine-*2′*-d_1 (**25**) from **20** due to the lability of the 2′

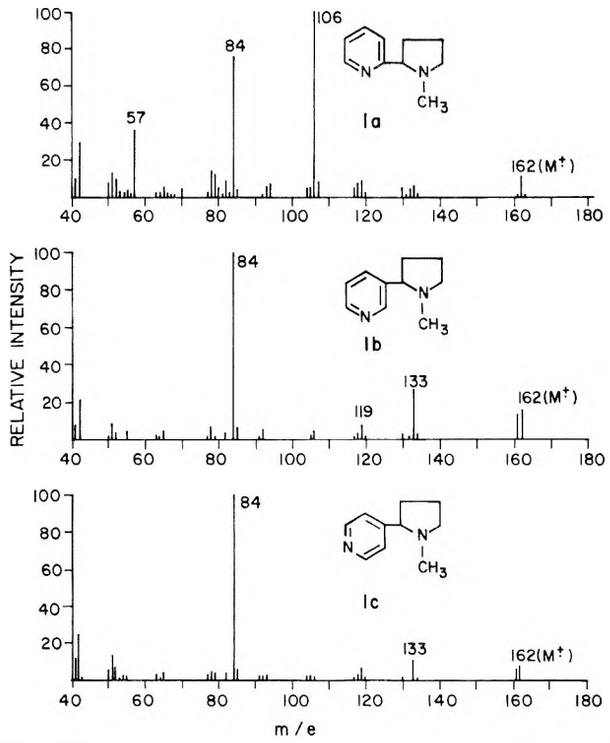


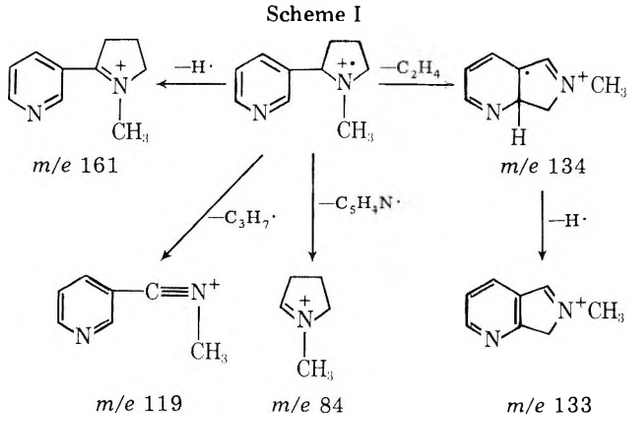
Figure 1. Mass spectra (70 eV) of 2-nicotine (**1a**), 3-nicotine (**1b**), and 4-nicotine (**1c**).

proton (deuteron). The milder reaction conditions of **2a** and DCO_2D or **20** and HCO_2H in the presence of dicyclohexylcarbodiimide proved effective, giving **24** and **25.** The 2-nornicotine-*N'*-d_1 (**19**) and the norcotinines-*N'*-d_1 (**33–35**) were prepared in the mass spectrometer from **2a** and **6a–c** by exchange with D_2O. The remaining deuterated analogues (**9–14** and **16–18**) were synthesized using the methods developed by Duffield et al.,[23] with minor modifications.

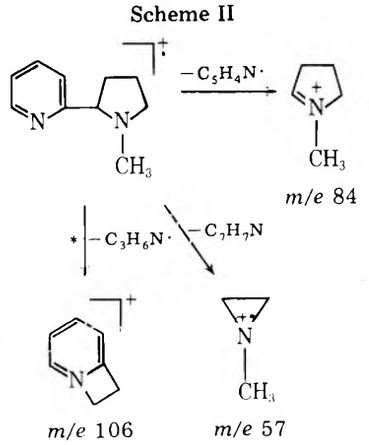
Mass Spectrometery. Recent studies have shown that during electron impact induced fragmentation the nitrogen atom in 2-substituted pyridines participates in unique fragmentation reactions.[24–28] The free-radical character of this nitrogen appears to be involved in bond-forming reactions,[29] which may occur in low yield, if at all, in 3- and 4-substituted pyridines. The mass spectrometry of the isomeric nicotinoids (**1a,c–6a,c**) has been neglected, although several investigators have conducted extensive studies on the tobacco alkaloids.[3a,23,30]

3-Nicotine (1b). The mass spectrum of 3-nicotine (Figure 1) has been discussed, and several mechanistic interpretations of the most abundant ions have appeared. The most complete investigation by Duffield et al.[23] and a direct analysis of daughter ions (DADI) study[30b] are combined to give the major

Scheme I



Scheme II



fragmentation pathways illustrated in Scheme I. The spectrum contains five major ions, three of which arise as a direct decomposition of the molecular ion (*m/e* 162).

The base peak in the spectrum occurs at *m/e* 84 (M − 78) due to the loss of the pyridyl moiety via α cleavage. The hydrogen atom lost to produce the M − 1 species comes 40% from the 2′ position, 15% from the 5′ position, and 10% from the 4′ position. The remaining 35% is postulated to come from the C-2, C-4, and/or C-3′ positions.[23] The peak at *m/e* 119 (M − 43) is the result of the loss of the 2′ proton with the 3′, 4′, and 5′ carbons and their attached hydrogens.

Formation of the *m/e* 133 (M − 29) ion has been shown by DADI to be a two-stage process. Ethylene, containing C-3′ and C-4′, is lost in the initial step from the molecular ion, and only after ring formation of *m/e* 134 is a proton lost from the 2 position of the pyridyl moiety.

2-Nicotine (1a). The dominant peak in the mass spectrum of 2-nicotine (Figure 1, Scheme II) occurs at *m/e* 106 (M − 56). The elemental composition of this ion was determined by high-resolution mass spectrometry to be $C_7H_8N^+\cdot$ (M − C_3H_6N), and metastable ion data indicate its formation from the molecular ion. The production of this ion requires the loss of the N′ CH_3 group and the 4′ and 5′ carbons and a hydrogen transfer from the leaving group to the charged moiety. The spectra of the deuterated analogues pinpoint the source of the transferred hydrogen to be 15% from the methyl, 24% from the 4′ position, and 61% from the 5′ position.

The reaction to form the *m/e* 106 ion demands participation of the pyridine nitrogen, and this ion is shown in Scheme II as a recyclization to the nitrogen. No metastable ions could be found to indicate its further fragmentation. The possibility has not been overlooked that this fragmentation could be initiated by a charge site different from that found in 3-nicotine.

A major peak in the spectrum is found at *m/e* 57 due to an ion having an elemental composition of $C_3H_7N^+\cdot$. This ion contains the 4′ and 5′ carbons and the N′ CH_3 group as well as their attached hydrogens. Other peaks found in the 2-nicotine spectrum are similar to those found in 3-nicotine. The abundant ion at *m/e* 84 is due to the loss of the pyridyl moiety via α cleavage.

4-Nicotine (1c). The mass spectrum of 4-nicotine (Figure 1) is, for the most part, identical with the spectrum of 3-nicotine. The only notable difference is that the α-cleavage reaction (M − 78) produces a higher percentage of the total ions formed than does this cleavage in the 3 isomer. Deuterium labeling, high-resolution results, and metastable data indicate the same mechanisms at work here as in the 3 isomer.

3-Nornicotine (2b). The mass spectrum of 3-nornicotine (Figure 2) contains a relatively abundant molecular ion and a more intense M − 1 species. The M − 1 peak has been shown by deuterium labeling to consist of a 55% loss of hydrogen from the 2′ position.[23] Lack of analogues deuterated in the 4′ or 5′

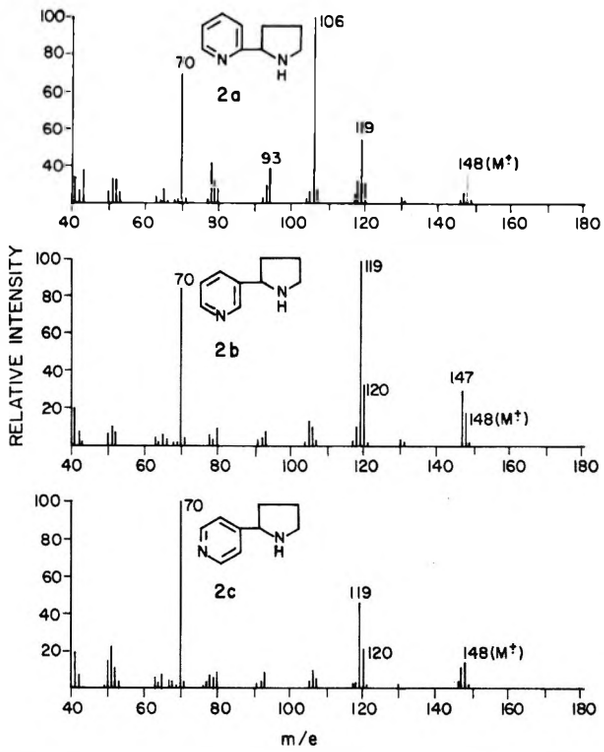


Figure 2. Mass spectra (70 eV) of 2-nornicotine (**2a**), 3-nornicotine (**2b**), and 4-nornicotine (**2c**).

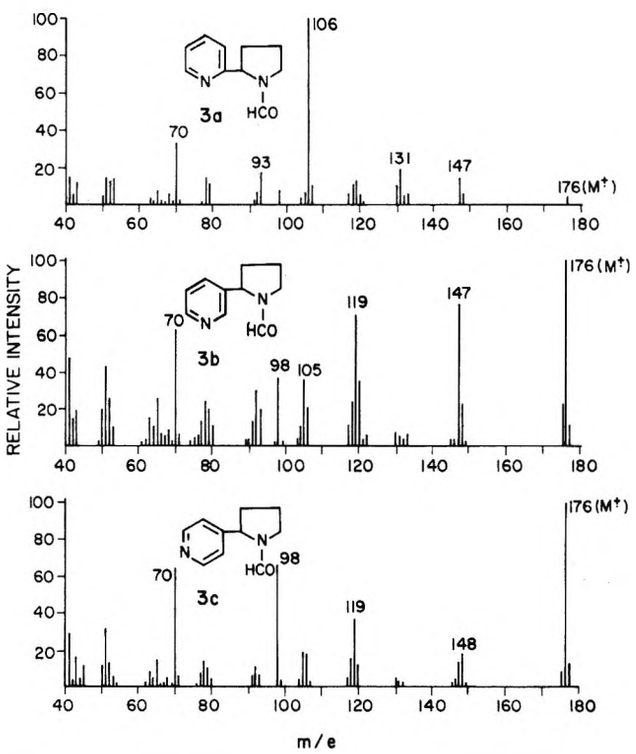


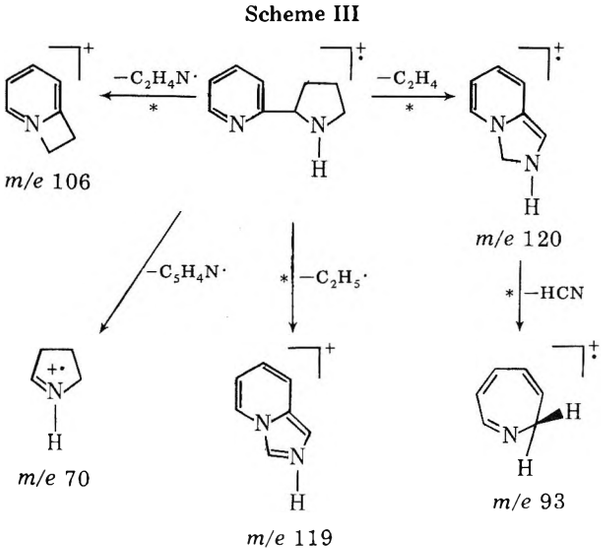
Figure 3. Mass spectra (70 eV) of *N'*-formyl-2-nornicotine (**3a**), *N'*-formyl-3-nornicotine (**3b**), and *N'*-formyl-4-nornicotine (**3c**).

positions precludes recognition of the other M − 1 species.

Similar to 3-nicotine, the 3-nornicotine spectrum contains an intense peak due to the loss of the pyridyl moiety producing the *m/e* 70 ion via α cleavage. The loss of 28 mass units from the molecular ion produces a peak at *m/e* 120 ($C_7H_8N_2^{+\cdot}$). The available deuterated analogues indicate the formation of this ion by the loss of ethylene containing the 3′ and 4′ carbons and their hydrogens.[23] The base peak of 3-nornicotine occurs at *m/e* 119 (M − C_2H_5) due to the loss of the 3′ and 4′ CH_2 groups and an additional hydrogen. This can occur either as a transfer of hydrogen to the leaving group or, by analogy to 3-nicotine, as the loss of hydrogen from the pyridine ring after cyclization of the *m/e* 120 ion.

2-Nornicotine (2a). The most abundant peak in the spectrum of 2-nornicotine (Figure 2, Scheme III) occurs at *m/e* 106. This ion has the same elemental composition as the *m/e* 106 ion found in 2-nicotine; in this case, however, it is due to the loss of C_2H_4N. Deuterium labeling indicates its formation

Scheme III



by the loss of the pyrrolidine nitrogen with the 4′ and 5′ carbons, hydrogen transfer to the charged species, and recyclization. The available deuterium analogues show 38% of the hydrogen transferred to be from the N′ position, and one can postulate the remainder to come from both the 4′ and 5′ positions, as was seen with 2-nicotine.

The mass spectrum contains a prominent α-cleavage product at *m/e* 70 and a relatively abundant *m/e* 119. A metastable ion indicates the formation of *m/e* 119 from the molecular ion, and deuterium analogues show its formation from *m/e* 120 via the loss of a 5′ hydrogen.

4-Nornicotine (2c). The mass spectrum of 4-nornicotine (Figure 2), as with 4-nicotine, shows that the further the substituent group from the pyridyl nitrogen, the more facile the α-cleavage. Here the α-cleavage product at *m/e* 70 has become the most abundant ion. No differences were found in the elemental compositions of the major ions from those of 3-nornicotine.

***N'*-Formyl-3-nornicotine (3b).** The electron impact induced fragmentation of *N'*-formyl-3-nornicotine includes many competing reactions (Scheme IV) which produce a complex spectrum (Figure 3). The most abundant ion is the molecular ion at *m/e* 176, from which only two major fragment ions are formed.

The first major ion is found at *m/e* 147 due mainly to the loss of CHO via simple cleavage. Ten percent of the ion abundance at *m/e* 147 is due to the loss of $C_2H_5\cdot$, presumably by the same mechanisms found in 3-nicotine involving the 3′ and 4′ carbons. The second major molecular ion fragmentation is due to the anticipated α cleavage, forming *m/e* 98. Loss of CO from *m/e* 98 leads to an *m/e* 70 fragment ion.

Large metastable ions indicate that both the expulsion of ethylene to form *m/e* 119 and the loss of $C_2H_3\cdot$ to give *m/e* 120 occur from the *m/e* 147 ion. While no deuterium analogues were available, the probability appears high that the 3′ and 4′ carbons are involved in these losses, considering the evidence found for the 2 isomer.

***N'*-Formyl-2-nornicotine (3a).** The mass spectrometric fragmentation of *N'*-formyl-2-nornicotine follows the same

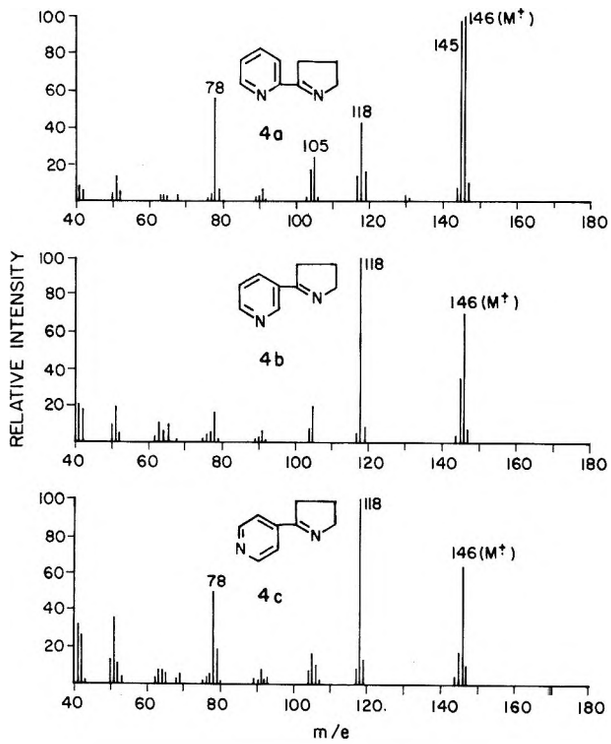
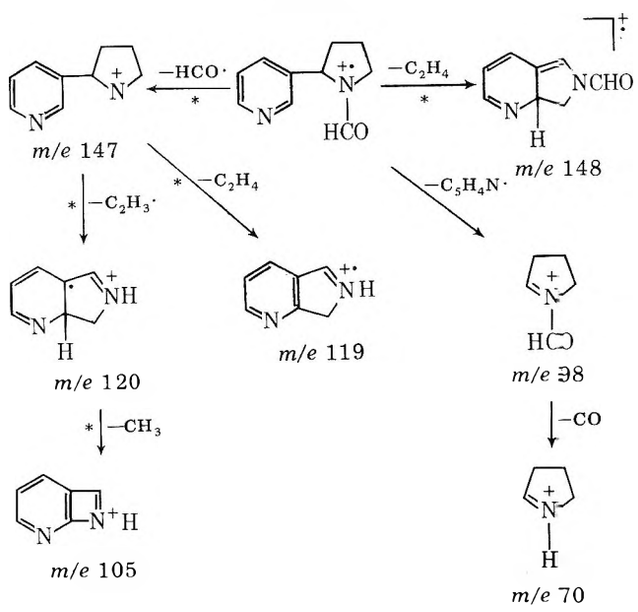


Figure 4. Mass spectra (70 eV) of 2-myosmine (**4a**), 3-myosmine (**4b**), and 4-myosmine (**4c**).

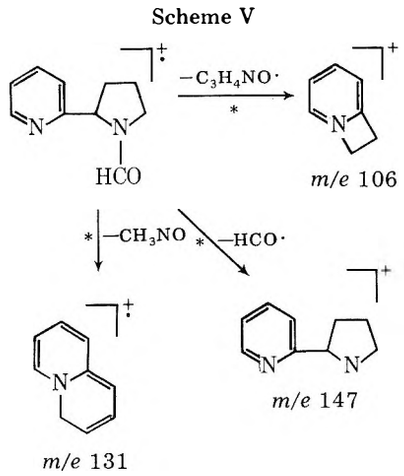
mechanism that has characterized the other 2 isomers of these nicotinoids. The most abundant ion in the spectrum (Figure 3) is found at *m/e* 106 due to the loss of $C_3H_4NO\cdot$ (Scheme V). Deuterium labeling shows that 25% of the hydrogen transferred in this reaction is from the formyl proton. The remaining 75% is postulated to come from both the 4′ and 5′ positions. A relatively abundant *m/e* 131 peak is present due to the loss of CH_3NO from *m/e* 176. This fragmentation requires the transfer of two hydrogens to the leaving group or a two-stage process. Approximately 50% of the hydrogens lost comes from the 3′ position. The remaining hydrogens may be lost from the 4′ position or, if cyclization occurs, the pyridine ring.

***N′*-Formyl-4-nornicotine (3c).** The mass spectrum of *N′*-formyl-4-nornicotine (Figure 3) closely resembles that of

Scheme IV



Scheme V



the 3 isomer insofar as the major peaks are concerned. As in other 4 isomers, the spectrum presents a marked increase in the α-cleavage product at the expense of the other ions, although the *m/e* 176 remains the most abundant ion.

3-Myosmine (4b). The mass spectrum of 3-myosmine (Figure 4) contains only three abundant peaks; the molecular ion, the M − 1 species, and the base peak at *m/e* 118. The loss of ethylene from M^+ to produce the most abundant ion at *m/e* 118 is due to the expulsion of C-3′ and C-4′ with their attached hydrogens.[23] It is noteworthy that α cleavage, which would result in the formation of an *m/e* 68 ion, is not a favored process since it would involve cleavage of a vinylic linkage.

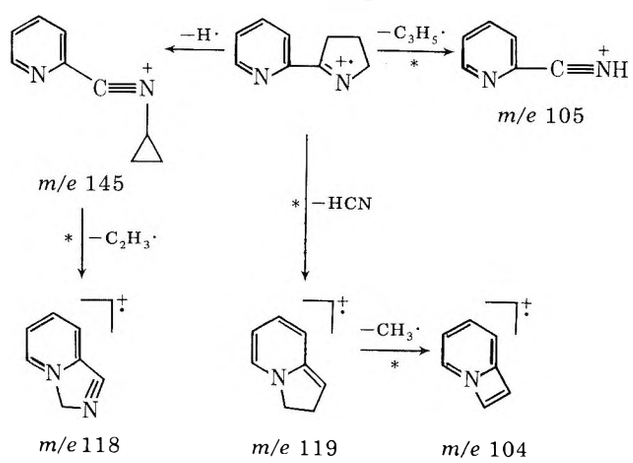
2-Myosmine (4a). The fragmentation of 2-myosmine produces a slightly more complex spectrum (Figure 4) than was found with the 3 and 4 isomers. The most abundant ion is now the molecular ion at *m/e* 146 (Scheme VI). A very stable M − 1 ion is formed involving the loss of a proton from the 4′ and/or 5′ position.

A large metastable ion suggests the formation of *m/e* 118 via the loss of $C_2H_3\cdot$ from *m/e* 145 (M − 1). Deuterium labeling shows that the 3′ position is always involved in this loss, and therefore by structural considerations the 4′ position is also. The peak at *m/e* 117 was found to be M − CH_3N rather than the loss of hydrogen from *m/e* 118. It was noted that approximately 30% of the hydrogen lost here involves the 3′ position.

The ion at *m/e* 119 is due to the loss of HCN from the molecular ion. The loss of $CH_3\cdot$, indicated by a metastable ion to be from *m/e* 119, results in the formation of *m/e* 104. The peak at *m/e* 105 is due to the loss of the 3′, 4′, and 5′ carbons from the molecular ion, and the major peak at *m/e* 78 was determined to be the pyridyl moiety.

4-Myosmine (4c). The mass spectrum of 4-myosmine

Scheme VI



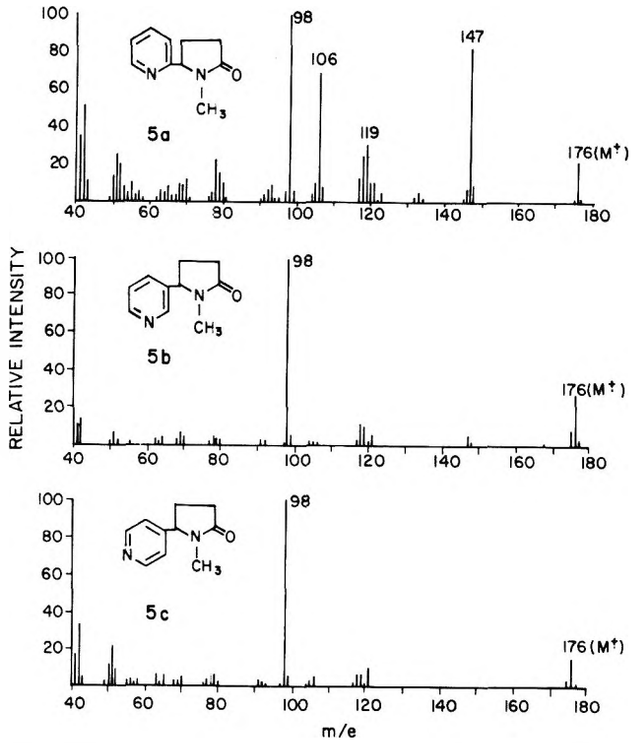


Figure 5. Mass spectra (70 eV) of 2-cotinine (**5a**), (*S*)-(−)-3-cotinine (**5b**), and 4-cotinine (**5c**).

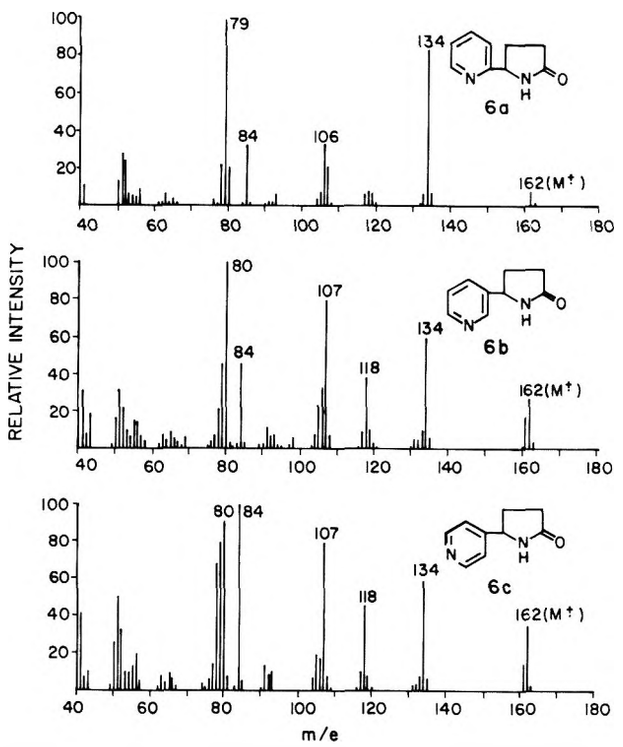


Figure 6. Mass spectra (70 eV) of 2-norcotinine (**6a**), (*S*)-(−)-3-norcotinine (**6b**), and 4-norcotinine (**6c**).

(Figure 4) contains the same major peaks found in the 3 isomer as well as the increased intensity of *m/e* 78 found in the 2 isomer. Clearly, the major structural influence in these three isomers is the vinylic linkage and not the position of pyridine substitution.

(*S*)-(−)-3-Cotinine (5b). The mass spectrum of (*S*)-(−)-3-cotinine (Figure 5) is dominated by the ion at *m/e* 98, and few other ions exceed 10% relative abundance. The *m/e* 98 ion corresponds to the loss of the pyridyl moiety via α cleavage. The spectrum contains a relatively abundant molecular ion at *m/e* 176, and the only other peaks of interest are found at *m/e* 118 and 119. The *m/e* 118 ion is due to the loss of $C_2H_4NO\cdot$ and *m/e* 119 to the loss of C_2H_3NO, both from the molecular ion.

2-Cotinine (5a). The mass spectrum of 2-cotinine (Figure 5) follows the pattern set by the other 2 isomers and demonstrates the influence of the pyridine nitrogen on its fragmentation mechanisms (Scheme VII). The expected peak at *m/e* 106 has the same elemental composition as found in the 2 isomers of nicotine, nornicotine, and *N'*-formylnornicotine. In this case, the peak at *m/e* 106 is not the most abundant ion.

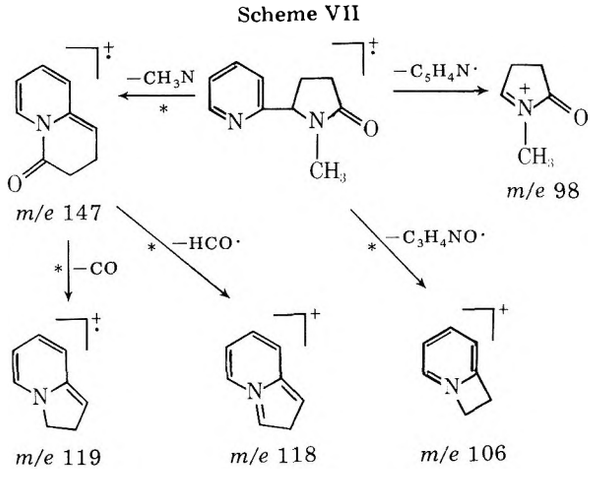
In 2-cotinine, the hydrogen transferred from the leaving group cannot come from the 5′ position. In fact, deuterium labeling shows that 100% of the hydrogen transferred comes from the methyl groups.

The α-cleavage product at *m/e* 98 remains the most abundant ion. A prominent ion at *m/e* 147 is due to the loss of the N′ CH_3 group. Further fragmentation of this ion results in the formation of the *m/e* 119 ion via the loss of CO and the *m/e* 118 ion from the loss of HCO·.

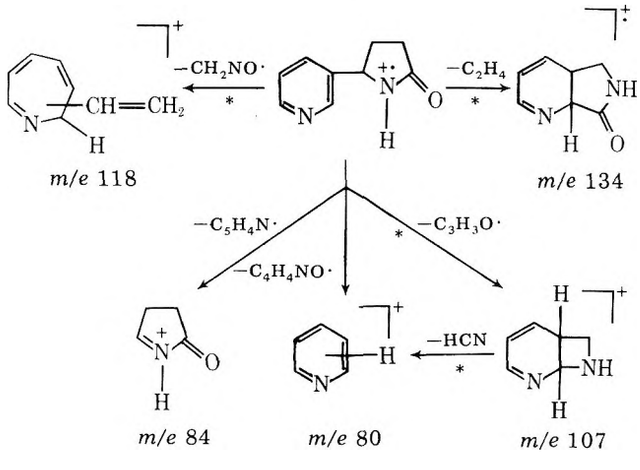
4-Cotinine (5c). The mass spectrum of 4-cotinine (Figure 5) contains the same peaks found in the 3 isomer. There is, as expected, an increase in the total number of ions formed by α cleavage.

(*S*)-(−)-3-Norcotinine (6b). The mass spectrum of (*S*)-(−)-3-norcotinine (Figure 6) is an anomaly among the 3-substituted pyridines presented here. While appearing to have every reason to undergo α cleavage to produce the base peak, the most abundant ion is found instead at *m/e* 80 (Scheme VIII). High-resolution data reveal this ion to be $C_5H_6N^+$, a protonated pyridine species. Deuterium exchange of the pyrrolidinone *N'*-hydrogen shows that 100% of this hydro n

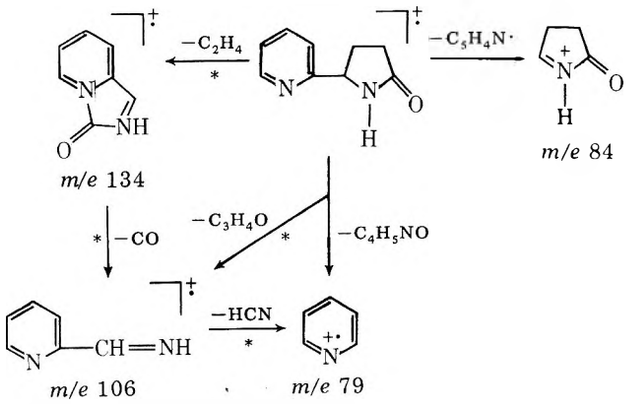
Scheme VII



Scheme VIII



Scheme IX



is transferred in the formation of the *m/e* 80 ion. The second hydrogen could not be identified due to the lack of deuterated analogues. The extreme ease with which the N′ proton is transferred to the pyridyl moiety relative to the other 3 isomers accounts for the low intensity of the α-cleavage product.

The α-cleavage product appears at *m/e* 84 and has an elemental composition of $C_4H_6NO^+$. Other fragment ions of interest include *m/e* 134, 118, and 107. The peak at *m/e* 134 is due to the loss of C_2H_4, presumably from the molecular ion and involving the loss of the 3′ and 4′ carbons. The ion at *m/e* 118 ($M - CH_2NO\cdot$) involves the transfer of a hydrogen from the 3′ position to the leaving group. The peak at *m/e* 107 ($M - C_3H_3O\cdot$) requires the transfer of a hydrogen from the leaving group. This proton can come from the 3′ and/or 4′ position.

2-Norcotinine (6a). The mass spectrum of 2-norcotinine (Figure 6) displays little indication of the expected pyridine nitrogen influence on the fragmentation mechanisms (Scheme IX). The expected formation of a $C_7H_8N^+$ ion ($M - C_2H_3NO$) does not occur. The peak at *m/e* 106 results from the loss of ethylene involving the expulsion of the 3′ and 4′ carbons followed by the loss of CO. This process appears favored over the loss of C_2H_3NO due to the stability of the neutral fragments generated. The major differences in this isomer relative to (*S*)-(−)-3-norcotinine are found in the marked decrease in intensity of *m/e* 118, 107, and 80 ions and the promotion of *m/e* 79 to become the base peak. This pyridine ion (*m/e* 79, $C_5H_5N^+\cdot$) involves the transfer of a hydrogen, 70% of which was found to come from the N′ position.

4-Norcotinine (6c). The mass spectrum of 4-norcotinine (Figure 6) contains the same major ions as were found in the 3 isomer. High-resolution data show them to have the same elemental compositions as found in 3-norcotinine. As with other 4 isomers, the α-cleavage product is more pronounced. In this case, *m/e* 84 has become the most abundant ion.

Summary

The electron impact induced fragmentation of these 2-substituted pyridines shows a marked influence of the pyridine nitrogen. Where structural limitations do not prohibit it, as in 2-myosmine and 2-norcotinine, this influence manifests itself in the production of an intense *m/e* 106 ion ($C_7H_8N^+$). The spectra of the 3 and 4 isomers are dominated by the α-cleavage product ($M - 78$), except in the case of the 3- and 4-myosmines and 3-norcotinine. The myosmines are prohibited from following the expected pathways by their vinylic linkage, 2-norcotinine by the stability of the neutral fragments formed, and (*S*)-(−)-3-norcotinine by the ease of hydrogen transfer from the pyrrolidinone.

Experimental Section

Melting points and boiling points are uncorrected. The ^1H NMR spectra were determined on either a Varian A60A or XL-100 spectrometer equipped with a Digilab FT accessory, with Me_4Si as an internal standard. The ^2H NMR spectra were run on the latter instrument using $CDCl_3$ as an internal standard. The structures of the isomeric nicotinoids (**1a,c–6a,c**) were confirmed by ^1H NMR spectroscopy, which will be reported elsewhere[20] with the ^1H and ^2H NMR analyses of the deuterated analogues. The IR spectra were run on either a Perkin-Elmer 621 or a Digilab FTS-14 spectrophotometer. The GLC and preparative GLC (PGLC) analyses were carried out using a Bendix 2300 instrument with 5 ft × 0.25 in stainless steel columns packed with 5% SE-30 on Chromosorb G-HP (80–100 mesh) with He carrier gas at 60 mL/min flow rate. The TLC and PTLC analyses were run on silica gel GF plates using $CHCl_3$/EtOH/NH_4OH (85:14:1) as the developing solvent. For PTLC purifications, after elution[31] and evaporation in air (ca. 1 h)[32] of solvent from the plates, the silica gel containing the desired compound was collected and washed with excess CH_2Cl_2 to eliminate trace impurities, care being taken to remove the majority of the CH_2Cl_2 without pulling much air through the gel. The silica gel was slurried with 10% HCl (ca. 10 mL per plate used) and the acid filtered off. The acid wash was repeated twice. The combined filtrates at <10 °C were basified with excess 50% NaOH (pH 11) and extracted with Et_2O. The Et_2O was dried[31] (NaOH) for 2–3 h and removed to give the desired compound, from which trace solvent was removed in 3–6 h under vacuum (0.1 mm). Low-resolution mass spectra were obtained on a CEC 21-104 mass spectrometer at 70 eV, 10 μA, 2000-V ion-accelerating voltage, and a source temperature of 250 °C. Accurate mass measurements were made on a CEC 21-110B with a resolution of 12 000. The metastable ion measurements were made by an accelerating voltage scan method similar to the one used by Schulze and Burlingame.[33]

2-(2-Pyrrolidinyl)pyridine (2-Nornicotine; 2a). To 4.35 g (0.03 mol) of cyclopropyl 2-pyridyl ketone[34] (**7a**) was added 4.0 g (0.089 mol) of $HCONH_2$, 1.2 g (0.0059 mol) of $MgSO_4 \cdot 6H_2O$, and 15 mL of 2-ethoxyethyl ether. The stirring mixture was heated at reflux under N_2 for 21 h, cooled (5 °C), and acidified (pH 2) with 25 mL of concentrated HCl. The solution was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 10% HCl (20 mL). The combined acid layers, after removal of traces of $CHCl_3$ under reduced pressure, were heated at reflux under N_2 for 16 h, cooled (5 °C), and basified with 50 mL of 50% NaOH (pH 11). The mixture was extracted with Et_2O. The Et_2O was dried (NaOH) and removed to give 1.49 g of an oil. The aqueous layer and insoluble solids were continuously extracted for 24 h with Et_2O. The Et_2O was dried (NaOH) and removed to give an additional 0.11 g of oil. The oil was distilled to give 1.31 g (30%) of crude **2a:** bp 60–65 °C (1.0 mm); GLC purity >70%. The distilled **2a** was dissolved in 100 mL of EtOH and treated with 6.1 g (0.027 mol) of picric acid. The mixture was stirred overnight. The picrate salt was collected, washed with EtOH, and air-dried. Two recrystallizations from H_2O gave 3.40 g of analytically pure dipicrate salt, mp 167–168 °C (lit.[35] mp 166 °C).

The dipicrate salt (3.0 g) was added to 50 mL of 10% NaOH, and the stirring mixture was heated at reflux under N_2 for 1.5 h. The solution was cooled (5 °C), treated with 20 mL of 50% NaOH (pH 11), and extracted with Et_2O (4 × 40 mL). The Et_2O was dried (NaOH) and removed to leave an oil which was distilled to give 0.65 g (88%) of analytically pure **2a:** bp 54 °C (0.24 mm) [lit.[35] bp 120 °C (12 mm)]; IR (neat) 3310 (NH), 2990, 2890, 1597, 1573, 1478, 1440, 780, 750 cm^{-1}.

4-(2-Pyrrolidinyl)pyridine (4-nornicotine; 2c) was prepared in 54% crude yield from cyclopropyl 4-pyridyl ketone[34] (**7c**) by the procedure used for the synthesis of crude **2a:**[32] bp 68–71 °C (0.02 mm); NMR purity, >90%. TLC showed a major component (**2c**), a minor component (**4c**), and two unidentified trace components. The product (**2c**) air-oxidized to **4c** on standing, and this coupled with the fact that it codistilled with **4c,** had the same GLC retention time as **4c** (12 columns), was partially oxidized to **4c** during PGLC, and corecrystallized as a dipicrate salt with the picrate salt of **4c** precluded the preparation of an analytically pure sample. However, **4c** of sufficient purity for spectral analysis was obtained by PTLC: IR (neat) 3300 (NH), 2970, 2880, 1602, 1413, 992, 815 cm^{-1}.

4-[1-(*N*-Phenylthiocarbonylimino)-2-pyrrolidinyl]pyridine. To 0.24 g (0.016 mmol) of freshly prepared **2c** (purity >90%) in 5 mL of dry benzene was added 265 μL (0.032 mol) of phenyl isothiocyanate, and the solution was allowed to stand overnight under N_2. The precipitated crystals were collected and air-dried to yield 0.33 g (74%) of the phenyl isothiocyanate derivative, mp 180–183 °C. Recrystallization from EtOH and drying in vacuo over P_2O_5 gave analytically pure material: mp 185.5–186.5 °C; IR (KBr) 3240 (NH), 2970, 1597, 1545, 1445, 1386, 1290, 750, 690 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.08 (m, 4, 3′- and 4′-CH_2), 3.87 (m, 2, 5′-CH_2), 5.66 (m, 1, 2′-CH_2), 7.24 (m, 7, phenyl H and 3- and 5-pyridyl H), 8.53 (m, 2, 2- and 6-pyridyl H), 9.04

(s, 1, NH).

2-(1-Methyl-2-pyrrolidinyl)pyridine (2-Nicotine; 1a). To a stirred solution of 1.39 g (27 mmol) of 88% HCO_2H and 1.08 g (13 mmol) of 36.9% H_2CO at 5 °C was added slowly 0.77 g (5.2 mmol) of **2a** in 1 mL of H_2O. The solution was heated at reflux under N_2 for 16 h, cooled (5 °C), and basified with 50% NaOH (pH 11). The mixture was extracted with Et_2O (4 × 10 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to leave 0.76 g (90%) of **1a** as an oil which on distillation afforded 0.69 g (82%) of analytically pure **1a:** bp 87–88 °C (4.2 mm) [lit.[35] bp 122 °C (24 mm)]; IR (neat) 2970, 2945, 2782, 1592, 1572, 1473, 1437, 1048, 781, 751 cm^{-1}.

4-(1-Methyl-2-pyrrolidinyl)pyridine (4-Nicotine; 1c). To a stirred solution of 4.17 g (0.08 mol) of 88% HCO_2H and 3.24 g (0.04 mol) of 36.9% H_2CO in 4 mL of H_2O at 5 °C under N_2 was added dropwise 2.36 g (0.016 mol) of freshly prepared **2c** (purity >90%) in 1 mL of H_2O. The solution was allowed to warm to room temperature over 20 min and was cautiously warmed with a water bath to ca. 50 °C, where gas evolution became quite vigorous. Heating was discontinued until after the vigorous reaction subsided and was then resumed at reflux for 5 h. The reaction mixture was cooled (5 °C), basified with 50% NaOH (pH 11), and extracted with Et_2O (4 × 15 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to afford 2.01 g of **1c** as an oil. Distillation gave 1.36 g (52%; >95% pure by GLC) of **1c:** bp 43–45 °C (0.006 mm) [lit.[14] bp 94–95 °C (67 mm)]. Analytically pure **1c** was obtained by PGLC: IR (neat) 2975, 2950, 2785, 1600, 1461, 1414, 1316, 1048, 993, and 820 cm^{-1}.

2-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-Formyl-2-nornicotine; 3a). To 4.35 g (0.03 mol) of cyclopropyl 2-pyridyl ketone[34] (**7a**) was added 4.0 g (0.089 mol) of $HCONH_2$, 1.2 g (0.0059 mol) of $MgCl_2{\cdot}6H_2O$, and 15 mL of 2-ethoxyethyl ether. The stirring mixture was heated at reflux under N_2 for 21 h. After cooling, the insoluble solids were broken up and the reaction was stirred with 50 mL of H_2O to give an aqueous/oil mixture which was extracted with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave an oil, which was distilled [66–74 °C (7 mm)] to remove the 2-ethoxyethyl ether and volatile impurities. Distillation of the residue afforded 1.79 g (34.4%) of **3a:** bp 99–101 °C (0.01 mm); GLC purity >89%. Analytically pure **3a** was obtained by PGLC: IR ($CHCl_3$) 1663 (C=O), 1595, 1437, 1419, 1382, 750 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.32; H, 7.06; N, 16.18.

3-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-formyl-3-nornicotine; 3b) was prepared in 54.6% yield from cyclopropyl 3-pyridyl ketone[34] (**7b**) by the procedure used for the synthesis of **3a:** bp 129–131 °C (0.03 mm) [lit.[36] bp 206 °C (10 mm)]; GLC purity >98%. An analytically pure sample of **3b** whose IR and NMR spectra were consistent with those reported[37] was prepared by PGLC.

4-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-formyl-4-nornicotine; 3c) was prepared in 52% yield from cyclopropyl 4-pyridyl ketone[34] (**7c**) by the procedure used for the synthesis of **3a:** bp 120–126 °C (0.25 mm); GLC purity >90%. The oil partially solidified on standing. Trituration of the solid with Et_2O gave a crystalline product (35%): mp 71–76 °C; GLC purity >98%. Analytically pure **3c** was prepared by sublimation [45–85 °C (0.02 mm)] followed by drying in vacuo over P_2O_5: mp 74–76 °C; IR ($CHCl_3$) 1668 (C=O), 1601, 1417, 1380 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.49; H, 6.96; N, 16.08.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (2-Myosmine, Apoferrorosamine; 4a). To a stirred solution of 22.0 g (0.2 mol) of diisopropylamine in 200 mL of anhydrous Et_2O at −65 °C under N_2 was added 43.7 g (0.15 mol) of a 2.2 M solution of *n*-butyllithium in hexane. The solution was stirred for 15 min, followed by the addition of 25.0 g (0.16 mol) of *N*-trimethylsilyl-2-pyrrolidone,[18] keeping the reaction below −60 °C. After stirring for 15 min, 15.1 g (0.1 mol) of ethyl picolinate was added with the mixture maintained below −60 °C. The reaction mixture was stirred at −65 °C for 15 min, allowed to warm to room temperature, and stirred overnight while a yellow solid precipitated. The mixture was cooled (5 °C) and acidified with 400 mL of 10% HCl (pH 2). The Et_2O layer was separated from the solid/aqueous acid mixture and washed with 50 mL of 10% HCl. The solid/aqueous acid layer and washings were combined and concentrated to 150 mL. The acid solution was heated at reflux for 18 h under N_2, cooled (5 °C), and basified with 50% NaOH (pH 10). The mixture was extracted with Et_2O (4 × 100 mL). The Et_2O was dried (Na_2SO_4) and removed to give 12.04 g of **4a** as a slightly gummy solid. Recrystallization from petroleum ether (30–60 °C) gave 10.1 g (67%) of **4a,** mp 48–50.5 °C. Pure **4a** was prepared by sublimation, 33–45 °C (0.02 mm), followed by drying in vacuo over P_2O_5, mp 52–53 °C (lit.[38] mp 46–49 °C). The IR and NMR spectra agreed with those reported.[38]

4-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (4-myosmine; 4c) was prepared from ethyl isonicotinate using the method described for the synthesis of **4a** with the following changes in the isolation and purification. The solid/aqueous layer and washing which resulted from the acidification of the reaction mixture were combined and heated at reflux under N_2 for 18 h. The solution was cooled (5 °C) and basified with 50% NaOH (pH 10). A solid separated, and the entire mixture was continuously extracted[39] with Et_2O for 24 h. The Et_2O was removed and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to give **4c** (81.5%, mp 86–89.5 °C). Recrystallization from petroleum ether (90–120 °C) or sublimation [40–54 °C (0.01 mm)] and drying in vacuo over P_2O_5 afforded pure **4c,** mp 89–90 °C (lit.[12b] mp 91 °C). The IR spectrum was consistent with that reported.[12b] As was found for 4b,[12a] pure **4c** is hygroscopic.

3-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (3-myosmine; 4b) was prepared in 82% yield from ethyl nicotinate by the method used for the synthesis of **4c,** mp 37–43 °C. The sample was sublimed [25–39 °C (0.01 mm)] and dried in vacuo over P_2O_5 to give pure **5b,** mp 40–44 °C (lit.[19] mp 44–45 °C). The IR and NMR spectra were identical with those reported for the natural base.[40]

Ethyl 3-(2-Pyridoyl)propionate (8a). To a stirred mixture of 9.8 g (0.2 mol) of NaCN in 200 mL of dry DMF at 15 °C was added 42.8 g (0.48 mol) of freshly distilled 2-pyridinecarboxaldehyde over 30 min. A deep red solution resulted to which, after it had warmed to room temperature, was added 38.8 g (0.4 mol) of freshly distilled ethyl acrylate over 1 h while keeping the reaction temperature from rising above 40 °C. The mixture was allowed to cool and stir for 2 h. It was poured into 1000 mL of H_2O and extracted with $CHCl_3$ (3 × 300 mL). The $CHCl_3$ was dried (Na_2SO_4) and removed to give an oil. Distillation [33–47 °C (7 mm)] removed the residual DMF and volatile impurities. The remaining oil precipitated a solid which was collected and discarded. The filtrate oil was distilled to afford 9.1 g (11%) of **8a:** bp 122–133 °C (0.09 mm); GLC purity >92%. Redistillation gave pure **8a:** bp 97–98 °C (0.07 mm) [lit.[17] bp 135–140 °C (0.2 mm)]; IR (neat) 2990, 1740 (ester C=O), 1705 (C=O), 1412, 1223, 1175, 1030, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 2.8 (m, 2, $-CH_2-$), 3.63 (m, 2, $-COCH_2-$), 4.23 (d, 2, J = 7 Hz, $-CO_2CH_2-$), 7.87 (m, 3, 3-, 4-, and 5-pyridyl H), 8.82 (m, 1, 6-pyridyl H).

Ethyl 3-(4-pyridoyl)propionate (8c) was prepared by reaction of 4-pyridinecarboxaldehyde with ethyl acrylate in the presence of NaCN as described for the synthesis of **8a.** Distillation [15–60 °C (10 mm)] of the crude reaction oil removed the residual DMF and volatile impurities. The remaining oil was distilled to yield analytically pure **8c** (33%): bp 123–125 °C (0.05 mm) [lit.[14,41] bp 145–147 °C (4 mm)]; IR (neat) 2995, 2940, 1743 (ester C=O), 1710 (C=O), 1592, 1443, 1218, 1165, 998, 778, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 2.8 (m, 2, $-CH_2CO_2-$), 3.38 (m, 2, $-COCH_2-$), 4.20 (d, 2, J = 7 Hz, $-CO_2CH_2-$), 7.86 (m, 2, 3- and 5-pyridyl H), 8.93 (m, 2, 2- and 6-pyridyl H).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.55; H, 6.14; N, 6.87.

1-Methyl-5-(2-pyridyl)-2-pyrrolidinone Monohydrate (2-Cotinine Monohydrate; 5a). To a solution of 6.21 g (0.03 mol) of **8a** and 17.7 g (0.3 mol) of $HCONHCH_3$ under anhydrous conditions (drybox) was added 0.29 g (0.003 mol) of anhydrous $MgCl_2$. The stirring mixture was heated at reflux under N_2 for 30 h. The mixture was cooled (5 °C), acidified (pH 2) with 10% HCl, and extracted with $CHCl_3$. The aqueous layer was cooled (5 °C), basified (pH 9) with 10% NaOH, stirred overnight, and then continuously extracted with Et_2O for 20 h. The Et_2O was removed. The residual oil was taken up in CH_2Cl_2 and dried (Na_2SO_4). Removal of the CH_2Cl_2 left an oil which was distilled to give 0.63 g (12%) of **5a:** bp 112–114 °C (0.03 mm); GLC purity >95%. PGLC afforded analytically pure **5a** as a monohydrate: IR (neat) 3470 (OH), 2960, 1787 (C=O), 1596, 1478, 1440, 1400, 1285, 1120, 996, 790, 755 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.68; H, 7.32; N, 14.61.

1-Methyl-5-(4-pyridyl)-2-pyrrolidinone monohydrate (4-cotinine monohydrate; 5c)[42] was prepared in 23% yield from **8c** by the procedure used for the synthesis of **5a.** The crude product was obtained as an oil which almost completely solidified on standing: bp 117–119 °C (0.02 mm); GLC purity >90%. PGLC gave analytically pure **5c** as a monohydrate: IR (neat) 3460 (OH), 3030, 2960, 1785 (C=O), 1601, 1417, 1400, 1310, 1118, 994, 817 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.78; H, 7.27; N, 14.33.

5-(2-Pyridyl)-2-pyrrolidinone (2-Norcotinine; 6a). To a mixture of 2.42 g (0.012 mol) of **8a** and 5.4 g (0.07 mol) of NH_4OAc in 80 mL of anhydrous MeOH was added 1.1 g (0.018 mol) of $NaBH_3CN$. The mixture was stirred under N_2 for 10 days. The reaction was cooled

(5 °C) and acidified with 10% HCl (pH 2). The MeOH was removed and the residue basified at 5 °C with 40 mL of 15% NaOH (pH 10). The mixture was stirred overnight at room temperature and then continuously extracted with Et_2O for 16 h. The Et_2O was dried (Na_2SO_4) and removed to give 278 mg (15%) of **6a** as a gummy solid, mp 83–92 °C. Recrystallization from cyclohexane/benzene (3:1) followed by drying in vacuo afforded an analytical sample: mp 96–97 °C; IR (KBr) 3240 (NH), 3110, 2985, 1690 and 1670 (lactone C=O), 1595, 1432, 1345, 1280, 1086, 992, 780, 757 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.56; H, 6.44; N, 17.09.

5-(4-Pyridyl)-2-pyrrolidinone (4-norcotinine; 6c) was prepared in 11% yield from **8c** by the method used for the synthesis of **6a**, mp 124–132 °C. Recrystallization from cyclohexane/benzene (2:1) and drying in vacuo gave analytically pure **6c**: mp 134–135.5 °C; IR (KBr) 3180 (NH), 3095, 2925, 1787 (C=O), 1603, 1156, 1068, 615, 600 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.69; H, 6.30; N, 17.17.

Deuterated Derivatives. All reaction apparatus were dried at 150–200 °C with a heat gun. All syntheses were run under N_2. The deuterated reagents used were as follows: D_2O (Bio-Rad Laboratories), 99.84 atom % enrichment; CH_3OD (Wilmad Glass Co., Inc.), 99 atom % enrichment; CF_3CO_2D (Wilmad Glass Co., Inc.), 99 atom % enrichment; CH_3CH_2OD (Diaprep, Inc.), 99 atom % enrichment; CD_3I (Diaprep, Inc.), 99+ atom % enrichment; $NaBD_4$ (Merck Sharp & Dohme Canada, Limited, Isotope Division), 98 atom % enrichment; DCO_2D (EM Laboratories, Inc.), >99 atom % enrichment; CD_3NH_2·HCl (EM Laboratories, Inc.), >99 atom % enrichment; and $LiAlD_4$ (Merck Sharp & Dohme Canada, Limited, Isotope Division), 99 atom % enrichment. The percent deuteration for all derivatives is given in Table I.

2-(1-Methyl-d_3-2-pyrrolidinyl)pyridine (2-Nicotine-*methyl*-d_3; 9). To a stirred mixture of 202 mg (1.36 mmol) of **2a** and 219 mg (1.59 mmol) of K_2CO_3 in 5 mL of pesticide grade CH_3CN was added 218 mg (1.50 mmol) of CD_3I. After stirring for 18 h, the solvent and unreacted CD_3I were removed [20 °C (15 mm)]. The residue was dissolved in 5 mL of H_2O, basified (pH 11) at 5 °C with 2 mL of 50% NaOH, and extracted with Et_2O (4 × 3 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to give 154 mg (67%) of **9**. GLC showed ca. 75% **9** and ca. 25% **2a**. PGLC gave spectroscopically pure **9**.

2-(1-Methyl-2-pyrrolidinyl-*2*-d_1)pyridine (2-Nicotine-*2'*-d_1; 10). To a cooled (5 °C), stirred solution of 175 mg (3.4 mmol) of 88% HCO_2H and 141 mg (1.7 mmol) of 36.9% H_2CO in 2 mL of H_2O was added 100 mg (0.67 mmol) of **20** in 1 mL of H_2O. The reaction was heated at reflux for 16 h, basified (pH 11) at 5 °C with 2 mL of 50% NaOH, and extracted with Et_2O (4 × 5 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to afford 57 mg (52%) of **10**. GLC showed ca. 97% **10** and ca. 3% **20**. PGLC gave spectroscopically pure **10**.

2-(1-Methyl-2-pyrrolidinyl-*3,3*-d_2)pyridine (2-nicotine-*3',3'*-d_2; 11) was prepared from **21** in 81% yield by the procedure used to synthesize **10**. GLC showed ca. 97% **11** and ca. 3% **21**. PGLC gave spectroscopically pure **11**.

2-(1-Methyl-2-pyrrolidinyl-*4,4*-d_2)pyridine (2-Nicotine-*4',4'*-d_2; 12). To a cooled (5 °C), stirred slurry of 173 mg (4.6 mmol) of $LiAlH_4$ in 25 mL of anhydrous Et_2O was added slowly 104 mg (0.58 mmol) of **31**. The stirred mixture was heated at reflux for 16 h, cooled (5 °C), treated slowly with 0.75 mL of H_2O, and stirred for 1 h. The insoluble salts were removed and washed with Et_2O. The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to yield 73 mg (77%) of **12**. GLC purity >90%. PGLC gave spectroscopically pure **12**.

2-(1-Methyl-2-pyrrolidinyl-*5,5*-d_2)pyridine (2-nicotine-*5',5'*-d_2; 13) was prepared in 95% yield by reaction of **5a** with $LiAlD_4$ by the method used to obtain **12**. GLC purity was >90%. PGLC gave spectroscopically pure **13**.

4-(1-Methyl-d_3-2-pyrrolidinyl)pyridine (4-nicotine-*methyl*-d_3; 14) was obtained from PTLC pure **2c** in 36% yield by the method used to prepare **9**. GLC showed ca. 70% **14**, ca. 18% **2c**, and two unidentified compounds. PGLC gave spectroscopically pure **14**.

4-(1-Methyl-2-pyrrolidinyl-*2*-d_1)pyridine (4-Nicotine-*2'*-d_1; 15). Treatment of 462 mg of crude **22**, which was synthesized from 500 mg (3.4 mmol) of **4c** as described subsequently, with 440 mg (3.1 mmol) of CH_3I as shown for the preparation of **9** gave 166 mg of a solid/oil mixture. TLC showed no **22**, and GLC showed ca. 86% **15** and ca. 14% **4c**. PGLC gave spectroscopically pure **15**.

4-(1-Methyl-2-pyrrolidinyl-*3,3*-d_2)pyridine (4-Nicotine-*3',3'*-d_2; 16). To a cooled (0 °C), stirred solution of 841 mg (16.1 mmol) of 88% HCO_2H and 665 mg (8.2 mmol) of 36.9% H_2CO in 5 mL of H_2O was added dropwise over 5 min 490 mg (3.3 mmol) of **23** in 4 mL of H_2O. The reaction mixture was allowed to warm to room temperature over 20 min, was heated at 50–55 °C with a water bath for 30 min, and then was heated at reflux for 5 h. The solution was cooled (5 °C), basified (pH 11) with 50% NaOH, and extracted with Et_2O (4 × 15 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to give 0.486 g (88%) of **16**. GLC purity was >95%. PGLC gave spectroscopically pure **16**.

4-(1-Methyl-2-pyrrolidinyl-*4,4*-d_2)pyridine (4-nicotine-*4',4'*-d_2; 17) was synthesized in 96% yield from **32** by the method used for the preparation of **12**. GLC purity was >95%. PGLC gave spectroscopically pure **17**.

4-(1-Methyl-2-pyrrolidinyl-*5,5*-d_2)pyridine (4-nicotine-*5',5'*-d_2; 18) was prepared in 92% yield from **5c** by the method reported for the synthesis of **13**. GLC purity was >85%. PGLC gave spectroscopically pure **18**.

2-(2-Pyrrolidinyl-*1*-d_1)pyridine (2-Nornicotine-*1'*-d_1; 19). After D_2O equilibration of the mass spectrometer, a D_2O slurry of **2a** was introduced into the inlet system to give **19**.

2-(2-Pyrrolidinyl-*2*-d_1)pyridine (2-Nornicotine-*2'*-d_1; 20). To a stirred solution of 1.0 g (6.8 mmol) of **4a** in 40 mL of EtOH was added 421 mg (10.0 mmol) of $NaBD_4$. The mixture was stirred at room temperature for 24 h and was then slowly acidified (pH 2) with 10% HCl at 5 °C. After stirring for 30 min, the EtOH was removed. The residue was basified (pH 11) at 5 °C with 5 mL of 50% NaOH and extracted with Et_2O (4 × 20 mL). The Et_2O was dried (NaOH) and removed to give 734 mg of **20**, which TLC showed contained a minor amount of **4a**. The **4a** was removed by PTLC, giving 395 mg (39%) of **20**. PGLC gave spectroscopically pure **20**.

2-(2-Pyrrolidinyl-*3,3*-d_2)pyridine (2-nornicotine-*3', 3'*-d_2; 21) was prepared from **28** by reduction with $NaBH_4$ in EtOD using the method given for the synthesis of **20**. The crude **21** was shown by TLC to contain a trace of **4a**/**28**, which was removed by PTLC to give 170 mg (29%) of **21**. PGLC gave spectroscopically pure **21**.

4-(2-Pyrrolidinyl-*2*-d_1)pyridine (4-nornicotine-*2'*-d_1; 22) was synthesized from **4c** by the method used for the preparation of **20**. TLC indicated that the crude **22** contained a minor amount of **4c**. PTLC gave spectroscopically pure **22** (38%).

4-(2-Pyrrolidinyl-*3,3*-d_2)pyridine (4-nornicotine-*3', 3'*-d_2; 23) was obtained from **29** by the method used for the preparation of **21**. TLC showed that the product contained no **29**, and after removing trace solvent under vacuum (0.1 mm) spectroscopically pure **23** (79%) was obtained.

2-(1-Formyl-d_1-2-pyrrolidinyl)pyridine (*N'*-Formyl-d_1-2-nornicotine; 24). To a stirred solution of 102 mg (0.69 mmol) of **2a** and 34 mg (0.71 mmol) of DCO_2D in 4 mL of CH_2Cl_2 was added 153 mg (0.74 mmol) of dicyclohexylcarbodiimide in 3 mL of CH_2Cl_2. After stirring for 30 min, TLC indicated that all of the **2a** had been consumed. The reaction mixture was treated with 2 mL of D_2O and stirred for 2 h. The insoluble solid was removed. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave 136 mg of **24**, which was contaminated with dicyclohexylurea. PGLC gave spectroscopically pure **24**.

2-(1-Formyl-2-pyrrolidinyl-*2*-d_1)pyridine (*N'*-formyl-2-nornicotine-*2'*-d_1; 25) was synthesized by the reaction of **20** with HCO_2H using the method given for the preparation of **24**. The crude **25** was contaminated with a small amount of dicyclohexylurea. PGLC gave spectroscopically pure **25**.

2-(1-Formyl-2-pyrrolidinyl-*3,3*-d_2)pyridine (*N'*-Formyl-2-nornicotine-*3',3'*-d_2; 26). To 299 mg (6.5 mmol) of HCO_2H (>97%) in a 1-mL Pierce Reacti-Vial at 5 °C was added 194 mg (0.99 mmol) of **21**.[43] The closed vial was heated on a steam bath for 16 h and cooled. The reaction solution was dissolved in 2 mL of H_2O, basified with saturated K_2CO_3 (pH 9), and extracted with Et_2O (4 × 2 mL). The Et_2O was dried (Na_2SO_4) and removed to leave 147 mg (83%) of **26**. GLC purity was >95%. PGLC gave spectroscopically pure **26**.

3-(1-Formyl-d_1-2-pyrrolidinyl)pyridine (*N'*-formyl-d_1-3-nornicotine; 27) was prepared in 45% yield by the reaction of **2b** with DCO_2D using the method described for the synthesis of **26**. GLC purity was >95%. PGLC gave spectroscopically pure **27**.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl-*4,4*-d_2)pyridine (2-Myosmine-*3',3'*-d_2; 28).[44] A stirred solution of 1.0 g (0.0068 mol) of **4a** in 22.6 g (0.685 mol) of MeOD was treated with 50 μL of CF_3CO_2D and heated for 16 h at 40 °C. The reaction was cooled (20 °C), and 50 mg of Na_2CO_3 was added. The mixture was stirred for 2 h, followed by removal of the MeOD to leave an oil. The oil was taken up in CH_2Cl_2 and the insoluble material removed. Removal of the CH_2Cl_2 left 0.85 g of a solid (mp 46–51 °C) which was sublimed [35–60 °C (0.035 mm)] and dried in vacuo over P_2O_5 to give 0.626 g (62%) of spectroscopically

pure **28**, mp 51–52 °C.

4-(3,4-Dihydro-2*H*-pyrrol-5-yl-*4,4-d*$_2$)pyridine (4-myosmine-*3′,3′-d*$_2$; 29) was synthesized from **4c** by the method used for the preparation of **28**. The dried product (mp 88–89 °C; 92%) was of sufficient purity for subsequent reaction. Spectroscopically pure **29** was obtained by sublimation [45–54 °C (0.04 mm)] and drying in vacuo over P_2O_5, mp 89–90 °C.

1-Methyl-*d*$_3$-5-(2-pyridyl)-2-pyrrolidinone (2-Cotinine-*methyl-d*$_3$; 30). A mixture of 826 mg (4.0 mmol) of **8a** and 975 mg (13.8 mmol) of CD_3NH_2·HCl in 50 mL of MeOH was treated with 375 mg (6.0 mmol) of $NaBH_3CN$ and stirred for 4 days at room temperature. The reaction mixture was acidified (pH 2) with 2.5 mL of 10% HCl and stirred for 2 h. After removal of the MeOH, the mixture was basified (pH 10) at 5 °C with 10 mL of 10% NaOH, stirred for 16 h at room temperature, and then continuously extracted with Et_2O for 16 h. The Et_2O was dried (Na_2SO_4) and removed to give 124 mg (17%) of **30**. GLC purity was >95%. PGLC gave spectroscopically pure **30**.

1-Methyl-5-(2-pyridyl)-2-pyrrolidinone-*3,3-d*$_2$ (2-Cotinine-*4′,4′-d*$_2$; 31). A stirred mixture of 502 mg (2.9 mmol) of **5a** and 500 mg (3.6 mmol) of K_2CO_3 in 10 mL (0.56 mol) of D_2O was heated at reflux for 12 days. The resulting solution was cooled and extracted with CH_2Cl_2 (4 × 10 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave 448 mg (87%) of **31**. GLC purity was >95%. PGLC gave spectroscopically pure **31**.

1-Methyl-5-(4-pyridyl)-2-pyrrolidinone-*3,3-d*$_2$ (4-Cotinine-*4′,4′-d*$_2$; 32). A stirred mixture of 251 mg (1.4 mmol) of **5c** and 200 mg (2.0 mmol) of $KHCO_3$ in 7 mL (0.39 mol) of D_2O was heated at reflux for 7 days. The solution was cooled and extracted with CH_2Cl_2 (4 × 5 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to yield 239 mg (96%) of **32**. GLC purity was >95%. PGLC gave spectroscopically pure **32**.

5-(2-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ (2-norcotinine-*1′-d*$_1$; 33) was prepared from **6a** by the method used to synthesize **19**.

(*S*)-(−)-5-(3-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ [(*S*)-(−)-3-norcotinine-*1′-d*$_1$; 34] was synthesized from **6b** by the method used to obtain **19**.

5-(4-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ (4-norcotinine-*1′-d*$_1$; 35) was obtained from **6c** by the method used to obtain **19**.

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Registry No.—**1a**, 23950-04-1; **1b**, 54-11-5; **1c**, 66269-72-5; **2a**, 66269-73-6; **2a** dipicrate, 66269-74-7; **2b**, 494-97-3; **2c**, 66269-75-8; **3a**, 66269-76-9; **3b**, 38840-03-8; **3c**, 66269-77-0; **4a**, 4593-27-5; **4b**, 532-12-7; **4c**, 66269-78-1; **5a**, 66269-79-2; **5b**, 486-56-6; **5c**, 66269-80-5; **6a**, 66269-81-6; **6b**, 5980-06-3; **6c**, 66269-82-7; **7a**, 57276-28-5; **7b**, 24966-13-0; **7c**, 39512-48-6; **8a**, 66269-83-8; **8c**, 66269-84-9; **9**, 66269-85-0; **10**, 66269-86-1; **11**, 66269-87-2; **12**, 66269-88-3; **13**, 66269-89-4; **14**, 66269-90-7; **15**, 66269-91-8; **16**, 66269-92-9; **17**, 66269-93-0; **18**, 62453-04-7; **19**, 66269-94-1; **20**, 66269-95-2; **21**, 66269-96-3; **22**, 66269-97-4; **23**, 66269-98-5; **24**, 66269-99-6; **25**, 66270-00-6; **26**, 66270-01-7; **27**, 66270-02-8; **28**, 66270-03-9; **29**, 66269-65-6; **30**, 66269-66-7; **31**, 66269-67-8; **32**, 66269-68-9; **33**, 66269-69-0; **34**, 66269-70-3; **35**, 66269-71-4; $HCONH_2$, 75-12-7; $HCONHCH_3$, 123-39-7; phenyl isothiocyanate, 103-72-0; 4-[1-(*N*-phenylthiocarbonylimino)-2-pyrrolidinyl]pyridine, 66322-96-1; *N*-trimethylsilyl-2-pyrrolidone, 14468-90-7; ethyl picolinate, 2524-52-9; ethyl isonicotinate, 1570-45-2; ethyl nicotinate, 614-18-6; 2-pyridinecarboxaldehyde, 1121-60-4; ethyl acrylate, 140-88-5; 4-pyridinecarboxaldehyde, 872-85-5.

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(41) Spectral data were not reported for **8c**.[36] The compound was characterized as an oxime.
(42) The unhydrated base has been prepared by Sugasawa.[14]
(43) The **21** used for this preparation was obtained from a repeat of the initial synthesis and was found by MS to be 84% d_2 and 12% d_1.[22]
(44) One of us acknowledges Dr. J. I. Seeman for discussions on this reaction.

C-5 Substituted Pyrimidine Nucleosides. 1. Synthesis of C-5 Allyl, Propyl, and Propenyl Uracil and Cytosine Nucleosides via Organopalladium Intermediates

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Reaction of 5-chloromercuriuracil nucleosides (**1a,b**) with allyl chloride in the presence of Li_2PdCl_4 gives 5-allyluridine (**2a**) and 5-allyl-2′-deoxyuridine (**2b**), respectively, in good yields with minimal purification. $RhCl_3$ and $Rh(Ph_3P)_3Cl$ do not catalyze this alkylation. Hydrogenation of these 5-allyluracil nucleosides (**2a,b**) to 5-propyluridine (**3a**) and 5-propyl-2′-deoxyuridine (**3b**) occurs readily with no reduction of the pyrimidine ring. Isomerization of **2b** to 5-(1-propenyl)-2′-deoxyuridine (**4**) is achieved in the presence of $Rh(Ph_3P)_3Cl$. A similar reaction sequence with 5-chloromercuricytosine nucleosides (**5a,b**) gives good yields of 5-allyl- and 5-propylcytidines (**6a** and **7a**, respectively) and 5-allyl-, 5-propyl-, and 5-(1-propenyl)-2′-deoxycytidines (**6b, 7b,** and **8**, respectively), none of which have been reported in the literature previously. Characterization of products includes melting point, ^1H NMR, UV, TLC, elemental analysis, and IR. The probable mechanism and potential biological activities are discussed briefly.

In addition to thymidine, many naturally occurring C-5 substituted pyrimidine nucleosides are found in the RNA and DNA of living organisms,[1-4] although the specific function of the C-5 modification is unknown for most of these. As chemotherapeutic agents many C-5 substituted pyrimidine nucleosides have been shown to exhibit activity against Herpes simplex[5] and vaccinia viruses;[6] one of these, 5-iodo-2′-deoxyuridine, is used clinically[7] against Herpes keratitis infections. Several C-5 substituted pyrimidine nucleosides have been shown to act with varying specificity as inhibitors of certain enzymes, such as the inhibition of nucleoside phosphorylase by 5-trifluoromethyl-2′-deoxyuridine[8] or the mild inhibition of deoxythymidine kinase from human acute myelocytic blast cells by 5-propyl-2′-deoxyuridine.[9] One modified nucleoside, 5-fluoro-2′-deoxyuridine, is an inhibitor of thymidylate synthetase after in vivo 5′-monophosphorylation. Others may act as competitive substrates for enzymes, and many, such as 5-ethyl-2′-deoxyuridine in *E. coli*,[10] may be directly incorporated into DNA.

Many C-5 alkylated uracil nucleosides, such as 5-allyl-2′-deoxyuridine[11] (**2b**) and 5-propyl-2′-deoxyuridine[12] (**3b**), have been synthesized and assayed for biological activity. Studies with 5-allyl-2′-deoxyuridine (**2b**) have shown the following: **2b** inhibits the growth of Herpes simplex virus (HSV) I and II, without being cytotoxic;[5,9] **2b** as its 5′-monophosphate exhibits only weak inhibition of deoxythymidylate synthetase;[13] and it was reported that **2b** also inhibits nucleoside phosphorylase[14] in HeLa cells as efficiently as 5-trifluoromethyl-2′-deoxyuridine.[8] (Recently it has been shown that **2b** is a competitive substrate for horse liver thymidine phosphorylase[15] rather than an inhibitor.) Biological assays of 5-propyl-2′-deoxyuridine (**3b**) have shown that **3b** weakly inhibits both mitochondrial and cytoplasmic deoxythymidine kinases of acute myelocytic blast cells.[9,16] It (**3b**) also inhibits growth of HSV I transformed HeLa cells which are deficient in deoxythymidine kinase, without being cytotoxic.[5] When *E. coli* is grown in the presence of **3b**, the *E. coli* show much more resistance to damage by UV light,[17] presumably due to less UV-induced dimerization after incorporation of **3b** into the DNA.

Like the corresponding halogenated 2′-deoxyuridines, the C-5 halogenated 2′-deoxycytidines show pronounced biological activity.[9,18] With the exception of 5-ethylcytidine and 5-ethyl-2′-deoxycytidine,[21] alkylated cytosine nucleosides with two or more carbons at C-5 have not been available for study, but in analogy to the alkylated uracil nucleosides the C-5 alkylated cytosine nucleosides may exhibit significant biological activity.

In light of their known and potential biological effects, much recent effort[11,12,19-28] has been directed towards the synthesis of C-5 substituted pyrimidine nucleosides. We have been particularly interested in obtaining nucleosides with carbon chains attached at C-5. Synthetic approaches to date have usually involved synthesis of a C-5 substituted pyrimidine and condensation of this with a suitably protected and activated sugar followed by deprotection and separation of the α and β anomers.[11,12,20-24] In order to overcome some of the drawbacks inherent in this procedure, we sought a general synthetic route beginning with the unprotected parent nucleosides. Recent results in this laboratory have established that pyrimidine nucleosides can be substituted at the C-5 position via organopalladium intermediates.[27,28] The 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b,** which are readily available from uridine, 2′-deoxyuridine, cytidine, and 2′-deoxycytidine,[25,26] respectively, can react with olefins in the presence of Pd(II) to give the corresponding C-5 alkylated nucleosides directly. Although this general coupling reaction is similar to the results seen with phenylmercuric chloride and allyl chloride in the presence of Pd(II),[29] some interesting differences are observed. The present paper describes the following: (1) the reaction of allyl chloride with the 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b** and Li_2PdCl_4 to form 5-allyluridine[27] (**2a**), 5-allyl-2′-deoxyuridine (**2b**), 5-allylcytidine (**6a**), and 5-allyl-2′-deoxycytidine (**6b**), respectively; (2) the subsequent reduction of these 5-allylpyrimidine nucleosides to 5-propyluridine (**3a**), 5-propyl-2′-

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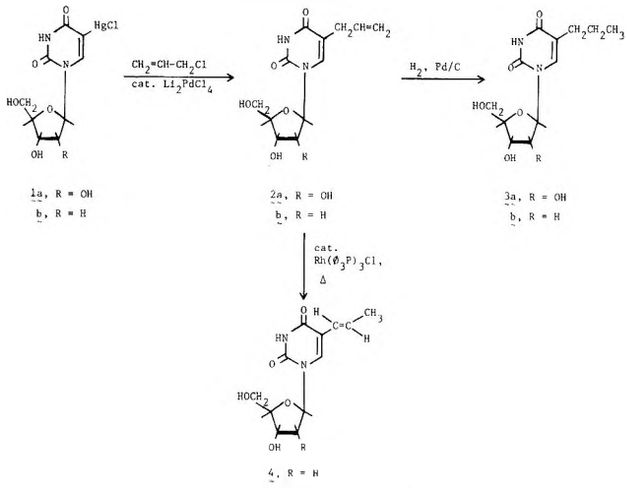
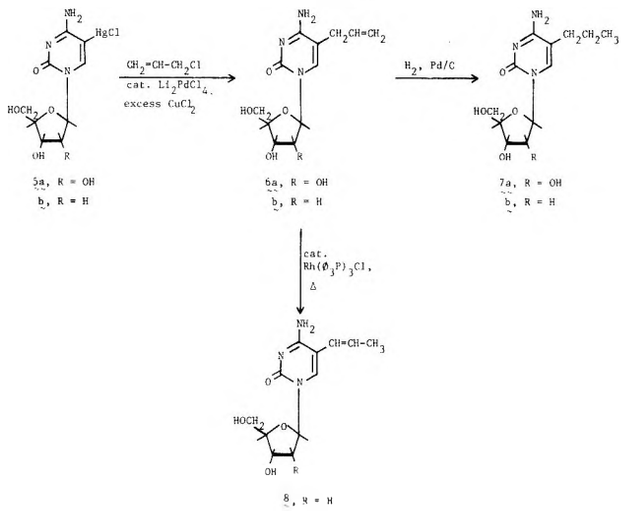
Scheme I



Scheme II



deoxyuridine (**3b**), 5-propylcytidine (**7a**), and 5-propyl-2′-deoxycytidine (**7b**), respectively; and (3) the conversion of the 5-allylpyrimidine nucleosides **2b** and **6b** to 5-(1-propenyl)-2′-deoxyuridine (**4**) and 5-(1-propenyl)-2′-deoxycytidine (**8**), respectively. This constitutes the first synthesis of 5-(1-propenyl)-2′-deoxyuridine (**4**) and 5-allyl-, 5-propyl-, and 5-(1-propenyl)cytosine nucleosides (**6**–**8**) reported in the literature to date.

Results and Discussion

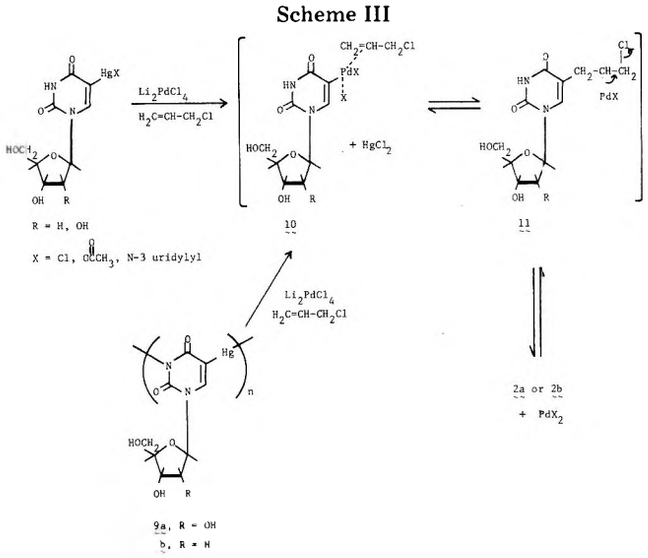
Reactions of C-5 Mercurated Nucleosides with Allyl Chloride. Our initial focal point was the investigation of the reactions of the mercuri nucleosides **1a,b** and **5a,b** with allyl chloride in the presence of palladium(II). When 5-chloromercuri-2′-deoxyuridine (**1b**) was suspended in methanol and allyl chloride and Li_2PdCl_4 were added, the insoluble mercuri nucleoside (**1b**) rapidly disappeared.[30] In this and related reactions the product was purified by precipitation of the metals as sulfides followed by column chromatography of the crude product on silica gel. The purified product was identified as 5-allyl-2′-deoxyuridine (**2b**) on the basis of ^1H NMR, melting point, IR, UV, elemental analysis, and comparison of these with the literature.[11] This and subsequent repetitions have given yields of 72–92% after column chromatography of the crude product.[31] The reaction of 5-chloromercuriuridine (**1a**) with allyl chloride in the presence of Li_2PdCl_4 goes with equal facility,[27] giving 5-allyluridine (**2a**) in 78–84% yields.[31] (See Scheme I.)

Due to the potential toxicity of the mercuri nucleosides and to further simplify the preparation of the 5-allyl nucleosides from the parent uracil nucleosides, we attempted to develop a "one-pot" procedure whereby uridine, for example, could be mercurated and then treated with allyl chloride and Li_2PdCl_4 to give **2a** directly. In pursuit of this goal, uridine and mercuric acetate were warmed in water for several hours, giving a thick white suspension of C-5 mercurated uridine.[26] Direct addition of allyl chloride and Li_2PdCl_4 in methanol at room temperature gave **2a** in 44% overall yield after purification by column chromatography, with 30% recovery of uridine. This method resulted in a lower overall yield of **2a** from uridine (44% vs. over 60% for the first method[32]), but it had the advantage of minimizing handling of the mercuriuridine necessary in the first method. This second, or "one-pot", method has also been applied in the synthesis of **2b** with an overall yield of 34% from 2′-deoxyuridine, again with recovery of substantial amounts of the parent nucleoside, 2′-deoxyuridine (ca. 20%). A repetition of this "one-pot" method with uridine in methanol rather than water as solvent resulted in less than 20% yield of **2a** with 75% of the material recovered as uridine. This is in agreement with earlier results which had suggested that the mercuration step proceeds much less efficiently in methanol than in water.[33]

The general pathway involved may be similar to that suggested for the reaction of phenylmercuric chloride with allyl chloride in the presence of Pd(II).[29] As indicated in Scheme III, the metal–metal exchange of Pd(II) for Hg(II) is apparently crucial for coupling of the allyl chloride to the mercuri nucleoside,[35] although the actual Pd(II) species reacting to form **10** may include a uridylyl species as a ligand(s). Binding studies have shown that Pd(II) can bind well to N-3 of thymidine or uridine in ratios of 1:2 at a pH well below that necessary for deprotonation,[34] and consequently any uridylyl species present may be serving as a ligand(s) for the Pd(II).[35] When **1a** was stirred with allyl chloride in methanol and no Pd(II) species were present, the insoluble[30] **1a** had not disappeared after 48 h at room temperature and an additional 72 h at reflux. Isolation of the white solid by filtration gave better than 94% recovery of a solid identified as **1a** by IR and NMR spectroscopy. With the exclusion of allyl chloride but in the presence of 1.1 equiv of Li_2PdCl_4, the insoluble[30] **1a** disappeared, but more slowly than in the presence of allyl chloride. Apparently the inclusion of an olefin in the reaction mixture is not necessary for the metal exchange, although its presence may increase the rate.

Activation of the C-5 position of uridine to increase the effective electron density is necessary to achieve olefin coupling, either by conversion to **1a** or a C-5 halogenated uridine. Reaction of **1a** or 5-iodouridine with methyl acrylate in the presence of Pd(II) has been shown[27,28] to give good yields (57

Scheme III



and 53%, respectively) of methyl 3-(5-uridylyl)propenoate. However, when uridine was stirred in methanol with an excess of methyl acrylate and 1.1 equiv of palladium acetate, the major product isolated after 40 h at room temperature was uridine in better than 75% recovery. No trace of the methyl 3-(5-uridylyl)propenoate was observed.

As indicated in Scheme III, the overall allylic coupling reaction is theoretically catalytic with respect to Pd(II). Experimentally, levels below 0.2 equiv of Li_2PdCl_4 per equiv of mercuri nucleoside result in decreased yields, even after extended periods of time. This has been noted in other similar reactions.[29] There appears to be at least two factors which might account for this partially catalytic behavior. (1) Pd(II) and allyl chloride can form inactive π-allyl complexes;[36,37] indeed, the formation of these complexes may be catalyzed by amines.[37] Although these π-allyl Pd(II) complexes are apparently not formed in anhydrous methanol,[36] enough may be formed due to trace water or the presence of mercury species, for example, to account for the less than catalytic behavior of the Pd(II) seen experimentally. (2) The other factor may be partial inactivation of Pd(II) due to binding at N-3 of the nucleosides,[34] although the pH of the reaction mixture is such that this effect should be weak. However, even if bound to N-3 of the nucleoside, the Pd(II) may still be able to catalyze the coupling reaction, as discussed earlier. Levels of Pd(II) as low as 0.02 equiv of Li_2PdCl_4 per equiv of mercuri nucleoside have been used with success if an excess of cupric chloride was included in the reaction mixture. Although Cu(II) apparently does not promote the allylation directly, it may minimize these and other factors limiting the catalytic behavior of Pd(II) by (1) serving as a one-electron acceptor for the reoxidation of any Pd(0) formed during the reaction or (2) by displacing any Pd(II) bound at N-3 of the nucleosides by competition and/or concentration effects since Cu(II),[38] as well as other metals,[39] has been shown to bind weakly at N-3 of uridine and thymidine. For example, when **1a** was reacted with allyl chloride in the presence of 0.02 equiv of Li_2PdCl_4 and 2.2 equiv of $CuCl_2$, purification gave a product identical with **2a** by ^1H NMR spectroscopy, TLC, and melting point in 64% yield. The reaction may also proceed satisfactorily with less than 1 equiv of cupric chloride. Although the inclusion of Cu(II) experimentally enhances the catalytic potential of Pd(II) in this reaction, the exact nature of the interaction has not been studied.[40]

Although most reactions of the mercuri nucleosides with olefins[27,28] have given products analogous to those obtained with phenylmercuric chloride and olefins,[29,41,42,45] one interesting exception is the reaction of 5-mercuriuridine[26] (**9a**) with allyl alcohol in the presence of Li_2PdCl_4. 3-(5-Uridylyl)-propionaldehyde was expected to be the major product by HPdX elimination from the intermediate analogous to **11**.[33,43] Little 5-allyluridine was expected. When 5-mercuriuridine[35] was reacted with 10 equiv of allyl alcohol in the presence of excess Li_2PdCl_4 in methanol, the only product recovered in greater than 60% yield after column chromatography on Sephadex G-25 was identical with 5-allyluridine (**2a**) by ^1H NMR spectroscopy and TLC in systems A, B, and C (see Experimental Section). None of the expected 3-(5-uridylyl)-propionaldehyde was detected. The 5-allyluridine (**2a**) may be formed by either elimination of HOPdX from the intermediate analogous to **11** to form **2a** directly or by formation of allyl chloride from the alcohol in situ and subsequent addition to form **2a**.[43]

Of even more interest synthetically is the reaction between 5-chloromercuricytidine[26] (**5a**) or 5-chloromercuri-2′-deoxycytidine[26] (**5b**) and allyl chloride. When **5b** was stirred in methanol with allyl chloride for 2.5 h in the presence of 0.24 equiv of Li_2PdCl_4 and 1.2 equiv of $CuCl_2$, the only product observed after purification was a white solid identified as 5-allyl-2′-deoxycytidine (**6b**) on the basis of melting point, ^1H NMR, IR, UV, and elemental analysis in 77% yield. This and subsequent repetitions have shown yields of **6b** to be 65–80%. Similarly, the reaction between **5a** and allyl chloride gave 5-allylcytidine (**6a**) in 70% yield. (See Scheme II.)

The synthesis of **6b** can also be accomplished directly from 2′-deoxycytidine (or its HCl salt) in a procedure similar to the "one-pot" method for synthesis of **2a** or **2b**, without isolating intermediates. The HCl salt of 2′-deoxycytidine was warmed with mercuric acetate in water and cooled, the solvent was removed to near dryness, and allyl chloride, Li_2PdCl_4, and $CuCl_2$ were added. Purification of the product gave a solid identified as **6b** on the basis of ^1H NMR spectroscopy and TLC in 53% yield after column chromatography. As noted earlier for uridine analogues, this "one-pot" method has the advantage of minimizing the handling of the presumably toxic mercuri nucleoside, but it results in lower overall yields from 2′-deoxycytidine (53% vs. 67% for the first method[44]).

Thus, the reactions of **5a** or **5b** with allyl chloride to form **6a** or **6b**, respectively, appear to proceed with a facility equal to that of the uridine series. These results are in contrast to those seen in the arylmercuric salt series.[45] When strong coordinating substituents such as amino groups are present when attempting to couple olefins to arylmercuric salts in the presence of Pd(II), the reaction does not proceed due to formation of an unreactive complex.[37,45] However, the exocyclic amino group of **5a** or **5b** does not appear to inhibit the allylation reaction, at least in the presence of excess cupric chloride. This may be due to direct competition of the copper species with Pd(II) for binding sites since Cu(II) has been shown to bind to N-3 and the C-2 exocyclic oxygen of cytidine simultaneously.[38] This competition would presumably free the Pd(II) from its unreactive complex and allow allylation to proceed. This supposition is borne out by the reaction of 5-acetoxymercuricytidine[46] with 10 equiv of allyl chloride and 1.1 equiv of Li_2PdCl_4 in methanol. With no copper species present, this reaction gave the desired **6a** in only 33% yield. When 1.1 equiv of cupric chloride is included and only 0.05 equiv of Li_2PdCl_4 is present, **6a** can be isolated in 60% yield. Apparently the inclusion of an excess of cupric chloride circumvents the inactivation of the Pd(II), allowing the palladium to regain its ability to catalyze the coupling reaction, even though ca. 0.2 equiv of Li_2PdCl_4 must still be used to maximize yields even in the presence of excess cupric chloride.

The choice of solvent and initial Pd(II) complex may also be important in obtaining **6a** or **6b** in reasonable yields. When 5-chloromercuri-2′-deoxycytidine (**5b**) was stirred in 40 mL of methanol at room temperature with 10 equiv of allyl chloride and 1.2 equiv of cupric chloride, the use of 15 mL of 0.1 N Na_2PdCl_4 (0.3 equiv) in water gave only a 26% yield of **6b**. Other results have shown that, although sodium salts are more easily removed from the product by column chromatography on silica gel than lithium salts, yields may be lower and reaction rates slower when using Na_2PdCl_4 as a catalyst rather than Li_2PdCl_4. The inclusion of water alone apparently causes a decrease in yields as well, perhaps due to the formation of inactive π-allyl complexes formed in aqueous solutions.[36]

Reduction of 5-Allylpyrimidine Nucleosides to the 5-Propyl Derivatives. The hydrogenation of 5-allyl nucleosides (**2a,b** and **6a,b**) under a hydrogen atmosphere using an active metal catalyst easily affords the 5-propyl nucleosides (**3a,b** and **7a,b**, respectively) in good purity and high yields (Table I). Crude unchromatogrammed 5-allyl nucleosides are resistant to reduction, apparently due to poisoning of the catalyst by residual sulfides; however, products which have undergone chromatography on silica gel or recrystallization reduce quickly with mild conditions.[47] (See Schemes I and II.)

Table I. Physical Properties and Yields of C-5 Substituted Pyrimidine Nucleosides

Compd	Registry no.	Mp, °C	UV[a] H+ λ_{max} (ϵ)	UV[a] H+ λ_{min} (ϵ)	UV[a] Stock solution λ_{max} (ϵ)	UV[a] Stock solution λ_{min} (ϵ)	UV[a] OH− λ_{max} (ϵ)	UV[a] OH− λ_{min} (ϵ)	TLC R_f in TLC system:[b] A	B	C	D	Yield, %
2a	59240-49-2	175.5	267 (9700)	234 (2600)	267 (9700)	234 (2500)	266 (7500)	247 (4900)	0.43	0.57	0.39	0.64	78
2b	73-39-2	126	267 (9490)	235 (2440)	267 (9540)	235 (2470)	266 (7400)	247 (5000)	0.54	0.69	0.46	0.68	72
3a	38971-54-9	197	267 (8960)	235 (1790)	267 (9090)	235 (1850)	266 (6840)	247 (4090)	0.43	0.60	0.38	0.66	78[c]
3b	27826-74-0	164	267 (8970)	235 (2310)	267 (8960)	235 (2270)	266 (7160)	246 (4670)	0.54	0.68	0.45	0.63	84[c]
4	66270-29-9	178	237 (12490), 293 (7920)	267 (4440)	237 (12540), 293 (7950)	267 (4450)	237 sh (14100), 288 (6590)	273 (5620)	0.55	0.72	0.47	0.69	87[c]
6a	66270-30-2	176	288 (11860)	248 (1270)	278 (8110)	254 (5090)	278 (8190)	255 (6270)	0.16	0.50	0.06	0.40	70
6b	66270-31-3	180	288 (12010)	247 (1140)	278 (8180)	254 (4860)	278 (8350)	254 (4960)	0.28	0.59		0.51	77
7a	66270-32-4	178[d]	288	245	278	256	278	256	0.18	0.52		0.41	92[c]
7b	66270-33-5	183	288 (12160)	245 (1070)	278 (8360)	254 (4710)	278 (8540)	254 (4700)	0.26	0.61		0.51	94[c]
8		157[d]	233 (11820), 298 (6610)	268 (2910)	233 sh (13230), 288 (5100)	271 (4120)	233 sh (13230), 288 (5470)	272 (4530)	0.29	0.64		0.54	40[c]

[a] UV spectra were obtained in aqueous solution at neutral pH, in dilute HCl (pH 1.2), and in dilute NaOH (pH 12.6); wavelengths are reported in nanometers. [b] Thin-layer chromatography (TLC) was accomplished on E. Merck precoated silica gel G60 F-254 (0.25 mm) plastic support TLC sheets (3 × 10 cm); elution was in 5 × 5 × 12 cm chambers lined with filter paper. Solvent systems: A, $CH_3OH/CHCl_3$ (1:3 v/v); B, *n*-BuOH/CH_3OH/concentrated NH_4OH/H_2O (60:20:1:20 v/v); C, CH_3OH/EtOAc (3:17 v/v); D, CH_3OH/EtOAc (3:2 v/v). [c] Yield from respective 5-allyl nucleoside. [d] Showed anomalous melting behavior (see Experimental Section for details).

Isomerization of 5-Allylpyrimidine Nucleosides to the 5-(1-Propenyl) Derivatives. Palladium(II) is known to catalyze the isomerization of allylbenzenes to propenylbenzenes.[29] In general, Pd(II), particularly $PdCl_4^{2-}$, is a very effective catalyst for the isomerization of terminal to internal olefins,[48] especially when conjugation energy is gained. However, in the synthesis of **2b** or **6b** from **1b** or **5b**, respectively, no traces of 5-(1-propenyl)-2′-deoxyuridine (**4**) or 5-(1-propenyl)-2′-deoxycytidine (**8**) are observed even after 72 h at reflux in the presence of Li_2PdCl_4. Since some success had been reported in the isomerization of allylbenzenes,[49] $Pd(CH_3CN)_2Cl_2$ was tried as a catalyst for the isomerization of 5-allyluridine (**2a**) to 5-(1-propenyl)uridine. When **2a** was refluxed in acetonitrile with 0.1 equiv of $Pd(CH_3CN)_2Cl_2$ and the reaction monitered by UV spectroscopy, the λ_{max} of **2a** at 266 nm had not shifted after 24 h, and ^1H NMR spectroscopy after purification showed the sole product to be recovered **2a.**

Some success has been reported using Wilkinson's catalyst [$Rh(Ph_3P)_3Cl$] as a reagent for the isomerization of allyl ethers to propenyl ethers.[50] When 5-allyl-2′-deoxyuridine (**2b**) was refluxed in 95% ethanol in the presence of 0.06 equiv of $Rh(Ph_3P)_3Cl$ and the reaction monitored by UV spectroscopy, the λ_{max} slowly shifted from the 267-nm peak of **2b** to 293 nm after 8 h. Evaporation, extraction of the residue with 10% aqueous ethanol, and column chromatography on Sephadex G-10 gave one major product, which was later identified as solely *trans*-5-(1-propenyl)-2′-deoxyuridine (**4**) on the basis of ^1H NMR, UV, IR, melting point, and elemental analysis in 87% yield. The results from ^1H NMR, UV, and TLC in systems A and B were identical with material identified as **4** which was prepared by the reaction of propene with **1b** in the presence of Li_2PdCl_4.[28]

The isomerization of 5-allyl-2′-deoxycytidine (**6b**) to 5-(1-propenyl)-2′-deoxycytidine (**8**) occurs as well, but with somewhat less facility. When **6b** was refluxed in ethanol with 0.2 equiv of $Rh(Ph_3P)_3Cl$ for 30 h, extraction and column chromatography on silica gel yielded an off-white solid. Recrystallization gave a white solid identified as **8** on the basis of ^1H NMR, UV, melting point, and elemental analysis. However, the yield before recrystallization was only 40%, perhaps due to inhibition of the reaction by the binding of rhodium at other sites, presumably at N-3 and the C-2 exocyclic oxygen similarly to other metals.[38,39] Close scrutiny of the ^1H NMR spectrum of **8** appears to indicate that the product may be a 1:3 mixture of cis and trans isomers. The ^1H NMR spectrum of the model compound propenylbenzene shows the $-CH_3$ of the propenyl moiety to be a doublet at δ 1.80 with J = 5.5 Hz for trans isomer,[51] while the *cis*-propenylbenzene gives a doublet at δ 1.72.[52] The ^1H NMR spectrum of **8** shows two doublets, one at δ 1.85 (J = 5 Hz) integrating for 2.25 protons and one at δ 1.74 integrating for 0.75 protons, which have been assigned to the propenyl $-CH_3$ protons of the trans and cis isomers, respectively. The C-6 proton of **8** apparently also exhibits a shift as a result of magnetic differentiation, being split into two unequal singlets at δ 7.95 (0.75 protons) and 7.72 (0.25 protons). The complexity of signals between δ 5.9 and 6.3 precludes any first-order analysis of the chemical shift for the vinylic protons[51,52] in assigning cis or trans stereochemistry.

Some effort has been directed toward developing a more direct synthesis of **4** or **8** from **1b** or **5b**, respectively. Presumably, coupling of allyl chloride with **1b** to give **2b** in the presence of a reagent able to catalyze the isomerization would result in the isolation of **4** directly. Palladium(II) is apparently not an efficient catalyst for the isomerization. Although rhodium(I) as Wilkinson's catalyst can catalyze the isomerization, neither rhodium(I) nor -(III) can accomplish the coupling reaction of allyl chloride to the mercuri nucleoside; both appear to catalyze the demercuration of **1a** or **1b** to uridine or

2′-deoxyuridine, respectively. These results agree with earlier observations; when **1b** is reacted with $Rh(CH_3)I_2(Ph_3P)_2$ in an attempt to methylate[53] **1b** and obtain thymidine, the only isolable nucleoside product is 2′-deoxyuridine. These and other approaches[54] to obtain the 5-(1-propenyl)pyrimidine nucleosides directly from the 5-mercuri nucleosides have not been pursued further at this time.

Conclusion

From the unprotected pyrimidine nucleosides, the mercuration and subsequent alkylation by coupling of the mercuri nucleoside to allyl chloride offer a facile method for the synthesis of the C-5 substituted uracil and cytosine nucleosides, most of which have not been reported elsewhere. The synthetic routes described in this paper have several advantages over any methods appearing in the literature to date: (1) coupling of allyl chloride to the nucleoside gives regiospecific addition at the olefin terminus to form only the C-5 allyl nucleoside (no isopropenyl isomers are observed); (2) the coupling reaction is nearly catalytic in Pd(II) rather than requiring equimolar amounts as with the coupling of olefins,[28,41,42,45] thus minimizing cost; (3) the isolation and purification of the alkylated nucleosides (particularly **4** and **8**) are much easier than when separating products obtained from reaction of the mercuri nucleosides with propylene and Pd(II),[28] and yields by this method are higher; (4) the allylic coupling reaction has potential use in the synthesis of longer and more complex substituents at C-5 of the pyrimidine nucleosides, particularly since the coupling reaction can tolerate many other functional groups;[28,41,42,45] and (5) the allylic coupling reaction gives 5-alkylated pyrimidine nucleosides in good yields after two or three steps, as opposed to many steps involved with consequent low yields for most of the approaches reported to date.[11,12,20-24] In addition, one of the major advantages of the alkylation method discussed in this paper over most prior syntheses is its ability to utilize the intact unprotected pyrimidine nucleosides as starting materials. This not only eliminates the protection–deprotection steps necessary otherwise, but also allows the use of the usually desired β anomer directly, circumventing the mixture of anomers obtained in many reactions. Consequently, this approach should be very useful synthetically in the introduction and elaboration of substituents at C-5 of uracil and cytosine nucleosides.

The reactions of 5-mercuripyrimidine nucleosides with more complex allylic halides in the presence of metals have been investigated and will be reported elsewhere.

Experimental Section

General. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-360 spectrometer in D_2O, and values reported are in ppm downfield from sodium 2,2,3,3-tetradeuterio-3-trimethylsilylpropionate as an internal standard. Quantitative UV spectra were recorded on a Cary 17 spectrophotometer in H_2O, and the pH indicated was obtained by diluting 20.00 mL of stock solution to 23.00 mL with 1.0 N HCl or 1.0 N NaOH (final pH approximately 1.2 or 12.6, respectively). IR spectra were recorded on a Beckman IR-8 in solid KBr using polystyrene for calibration. Elemental analyses were determined by Chemalytics, Inc., Tempe, Ariz. Thin-layer chromatography (TLC) was carried out using 3 × 10 cm E. Merck 60F-254 chromatogram sheets (0.25 mm silica gel) in 5 × 5 × 12 cm chambers lined with filter paper and four different TLC systems (relative proportions are v/v): system A, $CH_3OH/CHCl_3$ (1:3); system B, *n*-BuOH/CH_3OH/concentrated NH_4OH/H_2O (60:20:1:20); system C, CH_3OH/EtOAc (3:17); and system D, CH_3OH/EtOAc (3:2). Column chromatography was generally accomplished using Woelm activity I silica gel from ICN Pharmaceuticals (70–230 mesh) packed in 2-cm (i.d.) columns, and the column eluate was monitored using a LBK 8300 Unicord II UV detector. Hydrogenations were carried out at room temperature under a hydrogen atmosphere using 10% Pd/C from MCB as a catalyst. Evaporations were accomplished using Rinco rotating evaporators under an aspirator or a mechanical oil pump vacuum at 40 °C or lower. Final drying of products was done at 65 °C for 24 h over P_2O_5 at less than 0.1 mmHg. Low-resolution mass spectra consistent with the indicated structures have been obtained for compounds **2–4**.[55]

The mercuri nucleosides (**1a,b** and **5a,b**) were prepared by methods described elsewhere[26] from nucleosides purchased from Sigma and mercuric acetate purchased from Mallinckrodt. The allyl chloride was obtained from Aldrich (98% pure), the palladium(II) chloride from Matthey Bishop, and the tris(triphenylphosphine)chlororhodium from Eastman. Starting materials were used without further purification.

Data included in the table (UV spectroscopy and TLC) are not included in the Experimental Section.

General Allylation Procedure. The mercuri nucleoside to be allylated was weighed into a recovery flask, a designated volume of CH_3OH was added, and the solution was stirred at room temperature with a magnetic stirrer, with the insoluble mercuri nucleoside forming a thick white suspension. (If $CuCl_2$ was to be included, the designated amount was added at this point.) An exess of allyl chloride (usually 10–12 equiv) was pipetted in, followed by the addition of the indicated volume of 0.10 N Li_2PdCl_4 in CH_3OH (usually 0.2–0.3 equiv). The suspension was stirred for the designated time at room temperature, with all solid usually disappearing within the first 0.5 h. Hydrogen sulfide gas was bubbled through for less than 1 min, and the reaction mixture was vacuum filtered through Celite to remove the precipitated metal sulfides. The yellow filtrate was rotary evaporated to dryness, leaving an off-white solid.

Column chromatography was accomplished using a 2-cm (i.d.) column packed with the indicated amount of silica gel in $CHCl_3$. The product was added and eluted with a column volume of 5 vol % of CH_3OH in $CHCl_3$ (followed by a column volume of 10 vol % of CH_3OH in $CHCl_3$ for cytosine nucleosides). The column was then eluted with increasing vol % mixtures of CH_3OH in $CHCl_3$ in 1% increments. Each increment was about one-half the column volume, and the range of increments is indicated in the specific procedure. The eluate was collected in 7-mL fractions and monitored by absorbance at 254 nm. Fractions containing the major peak were combined, and the solvent was removed by rotary evaporation to leave the product as a white solid. The solid was then dried for 18–24 h at 65 °C at less than 0.1 mmHg pressure and weighed. Recrystallization was accomplished from the indicated solvent, and the product was washed with ether and dried. If the product did not recrystallize, the silica gel column treatment was repeated to remove residual impurities, and the product was dried and recrystallized as indicated.

5-Allyluridine (2a). Method A. A 3.29-g (6.87 mmol) sample of 5-chloromercuriuridine (**1a**) was stirred in 50 mL of CH_3OH and treated with 5.0 mL (61 mmol) of allyl chloride and 15 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.5 mmol) as described in the general allylation procedure. The reaction mixture was stirred overnight, treated with H_2S, and chromatographed on a column of 150 g of silica gel using increments of 8–18 vol % of CH_3OH in $CHCl_3$. The dried product was a white solid (1.52 g, 78%). Recrystallization from acetone or acetonitrile gave **2a** as white crystals: mp 175.5–176 °C (lit.[22] mp 175–176 °C); IR (KBr) 3405, 1703, 1655, 1460, 1270, 1100, 1040, 915 cm^{-1}; ^1H NMR (D_2O) δ 7.74 (s, 1), 5.94 (d, 1, J = 4 Hz), 5.90 (m, 1), 5.21 (dm, 1, J = 11 Hz), 5.19 (dm, 1, J = 17 Hz), 4.25 (m, 3), 3.88 (narrow m, 2), 3.07 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.59; H, 5.51; N, 9.82.

Method B. A 1.21-g (4.96 mmol) sample of uridine was dissolved in 5 mL of H_2O. A solution of 1.74 g (5.46 mmol) of mercuric acetate in 20 mL of H_2O was added, and the clear solution was stirred at 50 °C for 4 h. Sodium acetate (0.98 g, 7.2 mmol) was added. After 16 h, the solution cooled to room temperature, and 4.0 mL (50 mmol) of allyl chloride and 5.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.5 mmol) were added followed by the addition of 0.4 g (0.3 mmol) of $CuCl_2$. After 6 h, the grey suspension was treated with H_2S, filtered, and chromatographed on a column of 70 g of silica gel similar to method A. The dried product was a white solid (620 mg, 44% from uridine). Recrystallization from CH_3CN gave white crystals identical with product **2a** of method A by ^1H NMR spectroscopy, TLC, and melting point (370 mg of uridine (30%) was recovered from the column).

Method C. A 980-mg (2.0 mmol) portion of **1a** and 590 mg (4.4 mmol) of $CuCl_2$ were stirred in 15 mL of CH_3OH at room temperature. Then 0.5 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.05 mmol) and 1.7 mL (21 mmol) of allyl chloride were added. After 8 h, the solution was treated with H_2S and filtered, the solvent was removed from the filtrate, and the crude product was chromatographed on a column of 60

g of silica gel eluting with EtOAc/EtOH (4:1 v/v). The major product was an off-white solid (370 mg, 64%) identical with **2a** by ^{1}H NMR spectroscopy, TLC, and melting point.

5-Allyl-2′-deoxyuridine (2b). A 5.99-g (12.9 mmol) portion of 5-chloromercuri-2′-deoxyuridine (**1b**) was stirred in 125 mL of CH_3OH, 10.0 mL (123 mmol) of allyl chloride and 30 mL of 0.1 N Li_2PdCl_4 in CH_3OH (3.0 mmol) were added, and the solution was stirred for 3 h. Treatment with H_2S and chromatography on a column of 225 g of silica gel as outlined in the general allylation procedure using 8–18 vol % of CH_3OH in $CHCl_3$ gave a white solid (2.49 g, 72%) after drying. Recrystallization from CH_3CN yielded **2b** (1.9 g) as white crystals: mp 125.5–127.0 °C (lit.[11] mp 126–128 °C); IR (KBr) 3460, 1670, 1460, 1280, 1092, 760 cm^{-1}; ^{1}H NMR (D_2O) δ 7.70 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 5.9 (complex m, 1), 5.15 (dm, 1, J = 11 Hz), 5.08 (dm, 1, J = 17 Hz), 4.48 (m, 1), 4.03 (m, 1), 3.84 (narrow m, 2), 3.07 (d, 2, J = 6 Hz), 2.41 (dd, 2, J_1 = 5.5 Hz, J_2 = 7 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.87; H, 5.93; N, 10.51.

5-Propyluridine (3a). A solution of 302 mg (1.06 mmol) of 5-allyluridine (**2a**) in 10 mL of CH_3OH was pipetted into a 500-mL hydrogenation flask over 50 mg of 10% Pd/C and washed in with 15 mL of CH_3OH, and the system was sealed, evacuated with an aspirator, repressurized with 20 psig H_2, and stirred at room temperature for 1.5 h. The system was reevacuated, and the solution was gravity filtered to remove Pd/C. The solvent was removed from the clear filtrate by rotary evaporation and dried to leave a white solid (236 mg, 78%). Recrystallization from CH_3CN gave **3a** as white crystals: mp 197–198 °C; IR (KBr) 3540, 3440, 1660, 1470, 1274, 1100, 1055 cm^{-1}; ^{1}H NMR (D_2O) δ 7.79 (s, 1), 5.96 (narrow m, 1), 4.3 (complex m, 3), 3.91 (narrow m, 2), 2.30 (t, 2, J = 7 Hz), 1.5 (m, 2), 0.90 (t, 3, J = 6 Hz).

Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.27; H, 6.19; N, 9.80.

5-Propyl-2′-deoxyuridine (3b). A solution of 890 mg (3.3 mmol) of 5-allyl-2′-deoxyuridine (**2b**) in 30 mL of CH_3OH was put into a hydrogenation flask over 100 mg of 10% Pd/C. The system was sealed, evacuated, repressurized with 30 psig H_2, and stirred at room temperature for 6 h. The system was evacuated, the solution gravity filtered, and the solvent removed from the clear filtrate by rotary evaporation. The dried product was a white solid (760 mg, 84%). Recrystallization from CH_3CN or H_2O yielded **3b** as white crystals: mp 164.0–164.5 °C (lit.[12] 162 °C); ^{1}H NMR (D_2O) δ 7.70 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 4.52 (m, 1), 4.08 (m, 1), 3.84 (narrow m, 2), 2.33 (m, 4), 1.5 (m, 2), 0.90 (t, 3, J = 6 Hz).

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.03; H, 6.47; N, 10.06.

5-(1-Propenyl)-2′-deoxyuridine (4). A solution of 1.30 g (4.86 mmol) of 5-allyl-2′-deoxyuridine (**2b**) in 50 mL of 95% EtOH was stirred, $Rh(Ph_3P)_3Cl$ (278 mg, 0.3 mmol) was poured in slowly, a reflux condenser was added to the flask, and the mixture was heated to reflux in an oil bath. The reaction was monitored by UV adsorption, and after 8 h at reflux the λ_{max} had shifted from 266 to 293 nm. After 12 h at reflux, the mixture was cooled, concentrated to ca. 5 mL, and extracted four times with 20-mL portions of 10% EtOH. The 80 mL of 10% EtOH extract was concentrated to ca. 10 mL, giving a tan suspension. This suspension was chromatographed on a column (2 × 40 cm) of Sephadex G-10 eluting with 10% EtOH, and the eluate was monitored by UV spectroscopy at 254 nm, resulting in one major peak. Fractions contained in the peak were analyzed by TLC in system A, and fractions showing only one spot at R_f 0.54 were combined. The solvent was removed by rotary evaporation, leaving the dried product as a white solid (1.14 g, 87%). Recrystallization from CH_3CN yielded **4** as white crystals: mp 178.0–178.5 °C dec; IR (KBr) 3490, 3390, 3220, 1697, 1674, 1480, 1380, 1280, 1090, 1030, 978 cm^{-1}; ^{1}H NMR (D_2O) δ 8.24 (s, 1), 6.56 (t, 1, J = 6.5 Hz), 6.4 (broad m, 1), 6.3 (d, 1, J = 17 Hz, indicating trans stereochemistry), 4.69 (m, 1), 4.20 (m, 1), 3.98 (narrow m, 2), 2.43 (dd, 2, J_1 = 5.5 Hz, J_2 = 7 Hz), 1.85 (d, 3, J = 5.5 Hz).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.88; H, 5.95; N, 10.67.

5-Allylcytidine (6a). A 1.22-g (2.55 mmol) sample of 5-chloromercuricytidine (**5a**) was stirred in 40 mL of CH_3OH. As described in the general allylation procedure, 410 mg (3.1 mmol) of $CuCl_2$, 2.2 mL (27 mmol) of allyl chloride, and 6.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (0.6 mmol) were added consecutively, and the mixture was stirred for 7 h at room temperature. Treatment with H_2S and filtration were followed by neutralization with saturated $NaHCO_3$ solution. Chromatography on a column of 70 g of silica gel using increments of 18–28 vol % of CH_3OH in $CHCl_3$ followed by rotary evaporation gave the product as a white crystalline solid (510 mg, 70%). Recrystallization from CH_3CN yielded **6a** as white crystals: mp 176.0–176.5 °C dec; IR (KBr) 3400, 3220, 1655, 1600, 1480, 1295, 1105, 1055, 790 cm^{-1}; ^{1}H NMR (D_2O) δ 7.77 (s, 1), 6.0 (broad m, 1), 5.92 (narrow m, 1), 5.20 (dm, 1, J = 10 Hz), 5.12 (dm, 1, J = 18 Hz), 4.2 (complex m, 3), 3.88 (narrow m, 2), 3.11 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.97; H, 5.71; N, 14.65.

5-Allyl-2′-deoxycytidine (6b). Method A. A 2.84-g (6.14 mmol) portion of 5-chloromercuri-2′-deoxycytidine (**5b**) was stirred in 65 mL of CH_3OH. Cupric chloride (1.0 g, 7.4 mmol), 5.0 mL (61 mmol) of allyl chloride, and 15.0 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.5 mmol) were added consecutively as per the general allylation procedure. The mixture was stirred at room temperature for 2.5 h and then treated with H_2S, filtered, and chromatographed on a column of 82 g of silica gel using 18–28 vol % of CH_3OH in $CHCl_3$. The dried product was a white solid (1.26 g, 77%). Recrystallization from CH_3CN yielded **6b** as white crystals: mp 180.0–180.5 °C dec; IR (KBr) 3490, 3330, 1650, 1597, 1460, 1430, 1290, 1198, 1098, 1070, 1055, 1012, 920 cm^{-1}; ^{1}H NMR (D_2O) δ 7.77 (s, 1), 6.32 (t, 1, J = 6.5 Hz), 5.9 (broad m, 1), 5.23 (dm, 1, J = 10 Hz), 5.17 (dm, 1, J = 18 Hz), 4.49 (m, 1), 4.06 (m, 1), 3.85 (narrow m, 2), 3.14 (d, 2, J = 6 Hz), 2.35 (m, 2).

Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.87; H, 6.65; N, 15.42.

Method B. A 1.34-g (5.09 mmol) sample of 2′-deoxycytidine·HCl was dissolved in 10 mL of H_2O. Mercuric acetate (1.78 g, 5.4 mmol) was poured in slowly and washed in with 5 mL of H_2O, and the clear solution was heated to 75 °C in an oil bath. After 4.5 h, ca. three-fourths of the solvent was removed by rotary evaporation, and 25 mL of CH_3OH was added. Allyl chloride (4.5 mL, 55 mmol), 820 mg (6.1 mmol) of $CuCl_2$, and 12.8 mL of 0.1 N Li_2PdCl_4 in CH_3OH (1.28 mmol) were added consecutively while stirring at room temperature. After 4.0 h, the red solution was treated with H_2S, filtered, and chromatographed on a column of 80 g of silica gel eluting with increments of 18–28 vol % of CH_3OH in $CHCl_3$. The dried product is an off-white solid (720 mg, 53%). Repetition of the silica gel column treatment gave 360 mg (27% from 2′-deoxycytidine·HCl) of white solid identical with the product of method A (**6b**) by ^{1}H NMR spectroscopy, melting point and TLC in systems A and B.

5-Propylcytidine (7a). A solution of 104 mg (0.367 mmol) of 5-allylcytidine (**6a**) in 10 mL of CH_3OH was put into a 250-mL hydrogenation flask, and 25 mg of 10% Pd/C was added. The system was evacuated and repressurized with 20 psig H_2. It was stirred at room temperature for 3.0 h and filtered, and the solvent was removed by rotary evaporation. The dried product was a white solid (96 mg, 92%). Recrystallization from CH_3CN yielded **7a** as a white solid: upon heating, it gives off gas at 125–130 °C and chars at 178–182 °C; ^{1}H NMR (D_2O) δ 7.72 (s, 1), 5.95 (narrow m, 1), 4.3 (m, 3), 3.92 (narrow m, 2), 2.27 (t, 2, J = 7 Hz), 1.5 (m, 2), 0.92 (t, 3, J = 6.5 Hz).

Anal. Calcd for $C_{12}H_{19}N_3O_5 \cdot 0.25H_2O$: C, 49.69; H, 6.78; N, 14.48. Found: C, 49.61; H, 6.44; N, 14.07.

5-Propyl-2′-deoxycytidine (7b). A solution of 720 mg (2.7 mmol) of 5-allyl-2′-deoxycytidine (**6b**) in 10 mL of CH_3OH was pipetted into a hydrogenation flask over 50 mg of 10% Pd/C, and the flask was sealed. It was evacuated, repressurized with 20 psig H_2, stirred at room temperature for 2.0 h, and filtered, and the solvent was removed by rotary evaporation. The dried product was a white solid (680 mg, 94%). Recrystallization from EtOH gave **7b** as white crystals: mp 182.5–184.0 °C dec; ^{1}H NMR (D_2O) δ 7.75 (s, 1), 6.29 (t, 1, J = 6.5 Hz), 4.45 (m, 1), 4.09 (m, 1), 3.85 (narrow m, 2), 2.36 (m, 4), 1.53 (m, 2, J = 7 Hz), 0.91 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.45; H, 6.81; N, 15.90.

5-(1-Propenyl)-2′-deoxycytidine (8). A 637-mg (2.38 mmol) portion of 5-allyl-2′-deoxycytidine (**6b**) was dissolved in 20 mL of EtOH and stirred. Solid $Rh(Ph_3P)_3Cl$ (420 mg, 0.45 mmol) was slowly poured in and washed in well with 5 mL of EtOH, and the reaction mixture was brought to reflux. After 4 h at reflux, the λ_{max} had shifted from 278 to 291 nm. After 30 h at reflux, the reaction mixture was concentrated by rotary evaporation to 2–3 mL and extracted four times with 20-mL portions of hot H_2O, and the H_2O extract was centrifuged. The H_2O portions were combined, concentrated to leave an oil, and chromatographed on a column of 85 g of silica gel as described in the general procedure using increments of 18–26 vol % of CH_3OH in $CHCl_3$. The dried product was an off-white solid (252 mg, 40%). Recrystallization from 3% H_2O in acetonitrile gave **8** as white crystals which soften upon heating and slowly decompose above 157 °C: ^{1}H NMR (D_2O) δ 7.95 (s, 0.75, C-6 proton of trans isomer), 7.72 (s, 0.25, C-6 proton of cis isomer), 6.31 (t, 1, J = 6.5 Hz), 6.1 (narrow m, 2),[51] 4.48 (m, 1), 4.08 (m, 1), 3.87 (narrow m, 2), 2.35 (m, 2), 1.85 (d, 2.25, $-CH_3$ of *trans*-propenyl isomer, J = 5 Hz),[51] 1.74 (d, 0.75, $-CH_3$ of *cis*-propenyl isomer, J = 5 Hz).[52]

Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.84; H, 6.18; N, 16.02.

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Registry No.—**1a,** 58931-15-0; **1b,** 65505-76-2; 8 (*trans*-propenyl isomer), 66270-34-6; 8 (*cis*-propenyl isomer), 66270-35-7; allyl chloride, 107-05-1; uridine, 58-96-8; 2′-deoxycytidine·HCl, 3992-42-5.

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(31) The crude product after column chromatography shows a single spot on TLC and the absence of any structurally related nucleosides of similar chromatographic behavior by ^1H NMR spectroscopy. The material is suitable for further chemical transformations, but it usually must be rechromatographed or recrystallized to obtain analytically pure product due to the presence of residual inorganic salts.
(32) More than a 60% overall yield of **2a** from uridine for the first method is the result of 76% yield on mercuration (see ref 26) followed by 80% yield on coupling with allyl chloride.
(33) When the mercuration of uridine with mercuric acetate was carried out in methanol, the isolated **1a** appeared to have significant (10–30%) uridine as an impurity by ^1H NMR analysis.
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(53) A private communication from R. C. LaRock has indicated that $Rh(CH_3)I_2(Ph_3P)_2$ is a useful methylating agent for the alkylation of chloromercuribenzenes to toluene derivatives.
(54) An interesting synthesis of *trans*-propenylbenzene by methylation of styrene with CH_3Li in the presence of Pd(II) has been reported [but potential application to the synthesis of 5-(1-propenyl)pyrimidine nucleosides would require appropriately protected 5-vinyl nucleosides, which are not readily available]; see S.-I. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, **42,** 2870 (1977).
(55) Mass spectra of these and other alkylated pyrimidine nucleosides have been obtained and will be discussed in detail elsewhere.

Additions of Trialkyl Phosphites to Nitroalkenes

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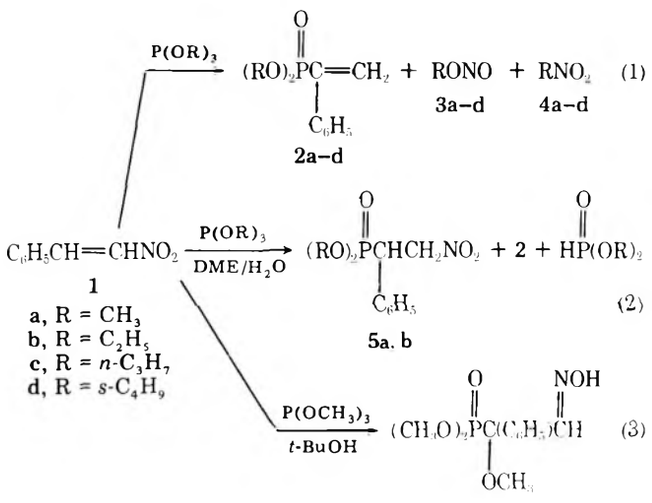
The reaction of β-nitrostyrene (**1**) with triethyl phosphite in DME gave diethyl α-styrylphosphonate (**2b**) in 85% yield. In DME/10% H_2O it gave a 50:50 mixture of **2b** and 1-diethoxyphosphinyl-1-phenyl-2-nitroethane (**5b**). In DME/10% D_2O with trimethyl phosphite it gave products with deuterium incorporated in the position β to the phenyl group in both **2a** and **5a**. Mechanistic implications are discussed.

Nitroalkenes may be regarded as the heteroatom analogues of α,β-unsaturated carbonyls. As such they may react by mechanisms involving attack at either nitro oxygen or at the β carbon. Attack at oxygen leads to deoxygenation and the products of a nitrene intermediate.[1] While there have been several reports that are consistent with attack at oxygen,[2] there has been none asserting attack at carbon.

Results and Discussion

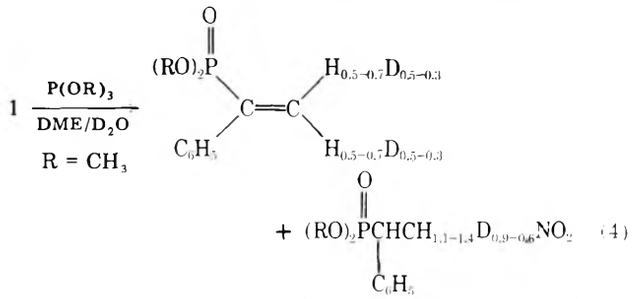
We have previously reported that the reaction of β-nitrostyrene (**1**) with trimethyl phosphite in *tert*-butyl alcohol gave 2-dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde oxime (**6a**).[3] We now wish to report that by varying the trialkyl phosphite and the solvent, two additional products can be obtained from reactions with **1** (Table I). We believe that these two (eq 1 and 2) involve a common intermediate and are the first examples of attack of trialkyl phosphites on the β carbon of nitroalkenes. Formation of the aldoxime **6a** (eq 3) may, but need not, involve attack at carbon.



The reaction of **1** with triethyl phosphite in 1,2-dimethoxyethane (DME) led to a clear, nonnitrogenous liquid that was shown by IR and NMR spectroscopy and independent synthesis to be diethyl α-styrylphosphonate (**2b**). Also isolated was ethyl nitrite (**3b**) (40%), as characterized by IR and NMR spectroscopy. It is likely that 40% does not accurately reflect the yield of nitrite since once formed ethyl nitrite could react with triethyl phosphite.[4] When the reaction was run without solvent (eq 1), both nitroethane (**4b**) and ethyl nitrite (**3b**) were isolated. This is in contrast with the reaction of *o*-dinitrobenzene with triethyl phosphite and with the pyrolysis of triethoxy(ethyl)phosphonium nitrite in which only ethyl nitrite was reported.[5] However, we have found that the former does give nitroethane (less than 1%) when reacted by general method B.

The reaction of **1** with trimethyl phosphite in DME with 10% water added (eq 2) gave a white solid which was shown by IR, NMR, and mass spectrometry to be 1-dimethoxyphosphinyl-1-phenyl-2-nitroethane (**5a**). Also formed were **2a** and dimethyl phosphonate. Attempts to interconvert **2, 5,** and **6** were unsuccessful.

The reaction of **1** with trimethyl phosphite in DME with 10% D_2O gave deuterated dimethyl α-styrylphosphonate (**2a**) (eq 4). Integration of the NMR spectrum indicated that 0.95



deuterium was incorporated (calcd max = 0.91) and was randomly distributed at the β position; thus the *E* and *Z* isomers were formed in approximately equal amounts. The mass spectrum of **2a** indicated that incorporation was at least 0.6 deuterium. Also formed was **5a** with deuterium incorporated at C-2 (β to the phenyl group). Integration of the NMR spectrum indicated 0.87 deuterium (calcd max = 0.91) was incorporated. In the complex signal for the methine hydrogen at C-1, a pair of triplets (δ 4.04) for the compound without deuterium at C-2 was visible along with two sets of two doublets (four lines each) for the two diastereomeric monodeuterated species. The mass spectrum indicated that the total incorporation at C-2 was at least 0.63 deuterium. There was no mass spectral nor NMR evidence for incorporation at C-1.

These results are consistent with a mechanism involving phosphorus attack at the electrophilic carbon of **1** (eq 5). The formation of **2** may then result from a 1,2-hydrogen shift[6] in

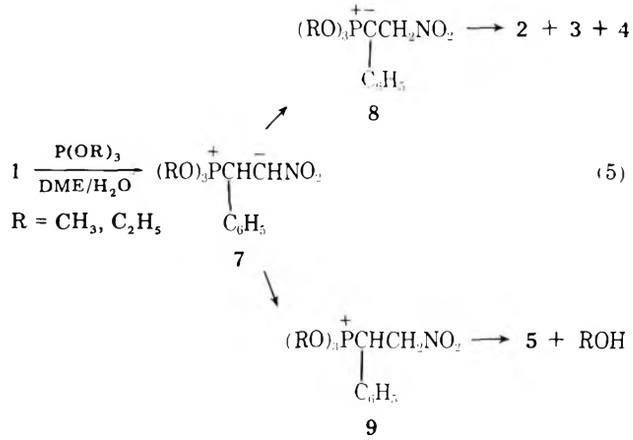


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Table I. Reactions of β-Nitrostyrene with Phosphites

R, $(RO)_3P$	Registry no.	Solvent	% yield[a] 2	Registry no.	6	Registry no.	Ratio[b] 3:4
CH_3	121-45-9	None	67	4844-39-7	7	42151-03-1	5.1
		DME	27		5[c]		
		DME/H_2O[d]	22				
		t-BuOH	Tr[c]		35		
C_2H_5	122-52-1	None	16	25944-64-3	32[c]	66324-33-2	5.6
		DME	85				
		DME/H_2O[e]	40				
		t-BuOH	25				
n-C_3H_7	923-99-9	None	60	66324-32-1	Tr[c]		4.9
s-C_4H_9	7504-61-2	None	77	66324-31-0	Tr[c]		6.5

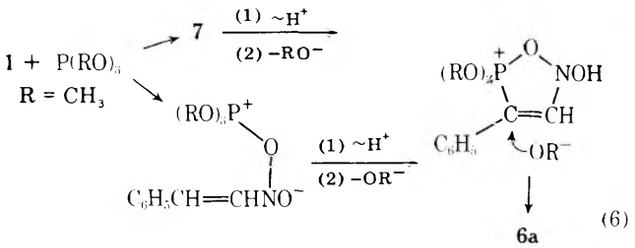
[a] Isolated yields. [b] Average of several trials. [c] Estimated by NMR. [d] Percent yield **5a** = 29. [e] Percent yield **5b** = 37.

the dipolar ion **7** to form an ylide, **8**. That this step is solvent assisted is supported by the high degree of deuterium incorporation in **2a**. Also an unassisted shift is unlikely since that would involve a cyclic four-electron antiaromatic transition state. The last step requires an Arbuzov-like dealkylation to form both alkyl nitrites and nitroalkanes. The essentially constant ratio of RONO/RNO_2 (Table I) suggests that there is little carbocation character in the alkyl group in this step.[5] And this is supported by the reaction of tri-*n*-propyl phosphite and **1** in which GC–mass spectral analysis of RONO and RNO_2 found no evidence for rearrangement of the *n*-propyl group.

The formation of **5** may result from protonation of either **7** or **8** to give a phosphonium salt **9** which is then dealkylated. The lack of deuterium incorporation at C-1 suggests, however, that **8** is not involved in the formation **5**.

The possibility that **8** and then **2** may be formed via **9** in DME/D_2O cannot be ruled out by these data since both would result in deuterium incorporation at C-2 of **2a**. But it seems unlikely to be an important pathway in dry DME in which **1** with triethyl phosphite gave 85% **2b** (Table I) to the exclusion of **5b**.

With respect to the formation of the aldoxime **6a**, it is possible to draw two relatively similar mechanisms for its formation involving either O or C attack as the first step (eq 6). Attack at carbon would lead to intermediate **7**. It is possible



(6)

then, but not required, that all three products, **2a**, **5a**, and **6a**, may be formed from a common intermediate.

Experimental Section[7]

General Method A. Diethyl α-Styrylphosphonate (2b). To a solution of 14.9 g (0.1 mol) of β-nitrostyrene (**1**)[8] in 100 mL of 1,2-dimethoxyethane (Eastman) was added 49.8 g (0.3 mol) of triethyl phosphite (Eastman). The mixture was stirred for 1 h, the solvent was removed on a rotary evaporator, and the residue was distilled to give 20.4 g (85%), bp 108–112 °C (0.5 mm), of **2b**: IR (CCl_4) 1280 (P=O), 1035 (POC), 840 cm^{-1} (=CH_2); NMR (CCl_4) δ 7.40 (m, 5, C_6H_5), 6.23 (pair of doublets, 1, c-PC=CH, J_{HH} = 1.9 Hz, J_{HP} = 24 Hz), 6.05 (pair of doublets, 1, *t*-PC=CH, J_{HH} = 1.9 Hz, J_{HP} = 42 Hz),[9] 4.02 (m, 4, OCH_2), 1.19 (m, 6, CCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 241 (3), 240 (23), 213 (5), 212 (32), 169 (3), 168 (23), 131 (46), 130 (82), 104 (73), 103 (100), 77 (57).

The reaction also produced 3.02 g (40%) of ethyl nitrite which was trapped with a dry ice–acetone cold finger distillation head placed at the top of a water jacketed condenser: NMR (CCl_4) δ 4.68 (q, 2, CH_2ONO), 132 (t, 3, CCH_3); IR (CCl_4) 1645 (s) and 1605 cm^{-1} (s) (ONO).

General Method B. Di-*n*-propyl α-Styrylphosphonate (2c). Tri-*n*-propyl phosphite[10] (23.7 g, 0.12 mol) was combined with 8.5 g (0.06 mol) of **1** in a 250-mL flask equipped with magnetic stirrer, thermometer, and distillation head. Downstream was a liquid nitrogen trap. The mixture was stirred at 0.07 mm and the temperature rose to 72 °C in 5 min, then fell to room temperature. After 2.5 h, 5.2 g of a green liquid was decanted from the N_2(l) trap. GC–mass spectral analysis showed the liquid to contain 3.6 g (40%) of *n*-propyl nitrite, 1.3 g (15%) of 1-nitropropane, and 0.7 g (11%) of 1-propanol. The presence of these compounds was confirmed by NMR spectroscopy; there was no evidence for the corresponding isopropyl compounds in either instance. The reaction mixture was then distilled to give 16.1 g (60%) of di-*n*-propyl α-styrylphosphonate (**2c**): bp 120–125 °C (0.09 mm); IR (cm^{-1}), 1280 (s, P=O), 1050 (vs, POC); mass spectrum, *m/e* (rel intensity) 268 (23.8), 226 (23.8), 184 (38.7), 103 (100), 77 (32.3); NMR (CCl_4) δ 0.93 (m, 6, CH_3), 1.57 (m, 4, CH_2), 3.85 and 3.97 (pair of triplets, 4, J_{HH} = 7.2 Hz, J_{HP} = 7.5 Hz), 5.99 (pair of doublets, 1, *t*-PC=CH, J_{HH} = 1.9 Hz, J_{HP} = 44 Hz), 6.12 (pair of doublets, 1, *c*-PC=CH, J_{HH} = 1.9 Hz, J_{HP} = 25 Hz), 7.4 (m, 5, C_6H_5).

General Method C. Dimethyl α-Styrylphosphonate (2a) and 1-Dimethoxyphosphinyl-1-phenyl-2-nitroethane (5a). To a solution of 14.9 g (0.1 mol) of **1** in 90 mL of DME and 10 mL of H_2O was added 42 g (0.34 mol) of trimethyl phosphite (Eastman). The reaction warmed to about 50 °C in 7 min before cooling to room temperature. After 2 h the solvent was removed by rotary evaporation and a 20.54-g fraction was collected by vacuum distillation and was shown by NMR spectroscopy to be dimethyl phosphonate. The residue was taken up in an equal volume of ether and slow crystallization began. Two crops were collected, combined, and recrystallized from carbon tetrachloride to give 7.51 g (29%), mp 104–106 °C, of **5a**: IR (mull) 1540 (NO_2), 1260 (P=O), 1040 cm^{-1} (POC); NMR ($CDCl_3$) δ 3.50 and 3.73 (pair of doublets, 6, $POCH_3$), 4.04 (pair of triplets, 1, CH, J_{HH} = 7.6 Hz, J_{HP} = 23.4 Hz), 4.96 (triplet, 2, CH_2, J_{HH} = J_{PH} = 7.6 Hz), 7.37 (singlet, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 260 (0.13), 259 (0.79), 213 (47), 212 (60), 181 (10), 117 (15), 116 (11), 110 (10), 109 (100), 105 (12), 104 (69), 103 (33), 93 (12), 91 (10), 77 (21).

The residue after filtration was stripped of solvent and distilled to give 4.7 g (22%) of **2a**: bp 103–107 °C (0.07 mm); IR (film) 1240 (P=O), 1045 cm^{-1} (POC); NMR (CCl_4) δ 3.66 (doublet, 6, J_{PH} = 11.2 Hz, OCH_3), 6.04 (pair of doublets, 1, J_{HH} = 1.5 Hz, J_{HP} = 45 Hz, *t*-PC=CH), 6.28 (pair of doublets, 1, J_{HH} = 1.3 Hz, J_{HP} = 24 Hz, *c*-PC=CH), 7.30 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 213 (10), 212 (64), 211 (34), 118 (12), 117 (57), 116 (48), 115 (45), 110 (31), 104 (43), 103 (100), 102 (36), 93 (38), 91 (40), 77 (68).

Method C with Deuterium Oxide. A 14.9-g (0.1 mol) sample of dried **1** was placed in a 500-mL three-neck flask equipped with condenser and pressure-equalizing dropping funnel, and the system was flushed with dry nitrogen for 0.25 h. A 90-mL sample of DME that had been refluxed over $LiAlH_4$ for 2 h was distilled directly into the flask before 10 mL of D_2O was added. Trimethyl phosphite (42 g, 0.34 mol) was then run in. The reaction mixture warmed noticeably. After 20 h the solvent was removed by rotary evaporation and the residue distilled to give a 19.4-g sample, bp 49–55 °C (0.08 mm), that was shown by NMR spectroscopy to be largely dimethyl phosphonate.[11] The remaining sample was taken up in an equal volume of ether and slow crystallization began. Two crops were collected to give 5.87 g (22%) of deuterated **5a** after recrystallization from CCl_4: mp 104–106 °C; NMR ($CDCl_3$) δ 3.50 and 3.73 (pair of doublets, 6, $POCH_3$), 4.04 (m, 1, CH), 4.96 (m, 1.13, CH_2NO_2), 7.35 (singlet, 5, C_6H_5); mass

spectrum (70 eV) *m/e* (rel intensity) 260 (0.85), 214 (48), 213 (79), 182 (10), 118 (11), 117 (14), 110 (9), 109 (100), 105 (44), 104 (39), 103 (115), 93 (10), 91 (7), 77 (10).

The residue after filtration was stripped of solvent and distilled to give a 3.48-g (16%) sample which was redistilled and a fraction of 1.27 g, bp 103–107 °C (0.07 mm), was taken: NMR ($CDCl_3$) δ 3.66 (doublet, 6, $POCH_3$), 5.75 and 6.26 (pair of doublets, 1.05, $PC{=}CH_2$), 7.30 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 214 (5), 213 (53), 212 (39), 118 (47), 117 (60), 116 (58), 115 (32), 110 (19), 109 (9), 105 (29), 104 (100), 103 (54), 102 (17), 93 (44), 91 (20), 77 (68).

Control with Diethyl α-Styrylphosphonate (2b). Triethyl phosphite (0.01 mol) and equimolar amounts of **2b** and **3b** were sealed in an NMR tube and heated at 50 °C for 2 h. The NMR spectrum was that of the individual components and remained unchanged after standing 1 month.

Control with 1-Dimethoxyphosphinyl-1-phenyl-2-nitroethane (5a). A 0.35-g sample of **5a** was mixed with 2 mL of trimethyl phosphite and 5 mL of DME and heated at 50 °C for 20 h. The solvent was removed under vacuum and the mixture solidified on standing. The solid was mixed with a small amount of ether and filtered to give 0.31 g (88%) of unchanged **5a**. There were no signals in the NMR spectrum for either **2a** or **6a**.[3]

Control with 2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde Oxime (6a). A 0.5-g sample of **6a** was mixed with 2 mL of trimethyl phosphite and 5 mL of DME and heated at 50 °C for 20 h. The low boiling materials were removed by vacuum distillation to leave a 0.55-g residue which on crystallization gave 0.35 g of unchanged **6a**. The remainder was shown by NMR to be free of **2a** and **5a**.

Synthesis of Diethyl α-Styrylphosphonate (2b). Diethyl α-styrylphosphonate (**2b**) was prepared from 3.68 g (20 mmol) of α-styrylphosphonic acid,[12] 7.15 g (43 mmol) of silver nitrate, and 2.24 g (40 mmol) of ethyl iodide according to the procedure of Werbel et al.[13] Distillation gave 3.25 g (67%) of **2b**, bp 108–112 °C (0.5 mm), whose IR and NMR spectra were identical in every respect with those of **2b** prepared from β-nitrostyrene.

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Registry No.—**1**, 102-96-5; **5a**, 37909-64-1; **5b**, 37909-65-2; ethyl nitrite, 109-95-5; propyl nitrite, 543-67-9; 1-nitropropane, 108-03-2; 1-propanol, 71-23-8.

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An Improved Procedure for the Addition of Dichloroketene to Unreactive Olefins[1]

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The cycloaddition of dichloroketene to hindered or unreactive olefins has, in the past, enjoyed only limited success. Not only are a large excess of the olefin or acid halide necessary, but the yields are often low. Most of these problems have now been overcome by dehalogenating trichloroacetyl chloride with activated zinc in the presence of the olefin and phosphorus oxychloride. Under these conditions, dichloroketene can even be added to tri- and tetrasubstituted olefins. An important feature of this procedure is that often only a small (5%) excess of acid chloride is necessary. The phosphorus oxychloride may function by complexing the zinc chloride produced in the reaction. Although styrene, which is normally polymerized by zinc salts, is transformed in good yield to the cyclobutanone adduct by this method, the very sensitive olefins dihydropyran and cyclopentadiene fail to yield isolable dichlorocyclobutanones.

Introduction

The cycloaddition of dichloroketene[2] to reactive olefins is a useful method for the synthesis of cyclobutanones. Certain of these dichlorocyclobutanones, for example, the adducts of indene[3] and various cyclopentadienes,[2a,4] are valuable precursors of tropolones. Many other synthetically useful transformations of cyclobutanones have been described[5] recently. Since dichloroketene is unstable and polymerizes readily, it is generated in situ in the presence of the olefin by (1) the dehydrohalogenation of a dichloroacetyl halide with an amine like triethylamine, or (2) the dehalogenation of a trichloroacetyl halide (usually trichloroacetyl bromide) with activated zinc (see eq 1 and 2). Both methods have certain

$$Cl_2CHC(=O)X \xrightarrow{Et_3N} Cl_2C{=}C{=}O + Et_3\overset{+}{N}H\overset{-}{X} \quad (1)$$

$$Cl_3CC(=O)X \xrightarrow{Zn\text{-}Cu} Cl_2C{=}C{=}O + ZnCl_2 \quad (2)$$

disadvantages. Tertiary amines and/or ammonium salts catalyze the decomposition of dichloroketene.[2b] The zinc dehalogenation method suffers from the fact that certain olefins, such as styrene, cyclopentadiene, or dihydropyran, are polymerized by zinc salts.[2b] With either method, a large excess of the olefin or acid halide is generally used.[2] Even with an excess

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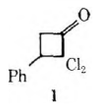
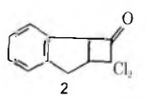
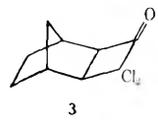
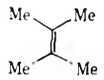
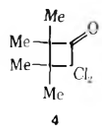
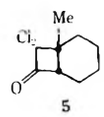
Table I. Generation of Dichloroketene from Trichloroacetyl Chloride and Activated Zinc in the Presence of Selected Olefins and Phosphorus Oxychloride

Olefin	Registry no.	Product	Registry no.	Yield, %[a]	Previous yield, %
	100-42-5	 1	13866-28-9	87	19[2b]
	95-13-6	 2	7316-61-2	81	12[3] 41[3c]
	498-66-8	 3	57774-86-4	70	10[2d]
	563-79-1	 4	66239-90-5	41	—
	591-49-1	 5	52809-65-1	79	(not reported)[11]
6	15910-23-3	7	26612-84-0	78	75[6]
8	66288-85-5	9	66239-91-6	72	—

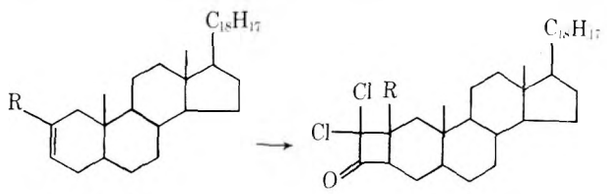
[a] Yield refers to purified product; yield of crude product was higher.

of reagent, however, yields of dichlorocyclobutanones from hindered olefins are often low or nil.

In cycloadditions to unreactive olefins, for example 2-cholestene (**6**) or 4-*tert*-butylcyclohexene, we[2e,6] have found it necessary to generate dichloroketene via the zinc dehalogenation procedure. The use of trichloroacetyl bromide, which fumes in the air and has to be freshly prepared and distilled at 135–136 °C, often gave irreproducible results.

Results and Advantages

Although most reports in the literature[2] in which the dichloroketene is generated by the zinc dehalogenation procedure have utilized trichloroacetyl bromide, we have now found that the commercially available[7,8] and more stable acid chloride is preferable and can be used in lower stoichiometric amounts (i.e., 2 equiv of acid chloride instead of 5 equiv of the acid bromide produce comparable yields (70–80%) of **7**).



6, R = H
8, R = CH_3

7, R = H
9, R = CH_3

Our more notable finding is that the addition of phosphorus oxychloride to the reaction mixture of zinc, trichloroacetyl chloride, and the olefin facilitates product isolation in all cases and leads to a dramatic improvement in yield in several cases (see Table I). Some advantages derived from the presence of $POCl_3$ are enumerated below.

When trichloroacetyl chloride was added to a stirred suspension of activated zinc and an olefin in ether, the reaction was quite exothermic and the solution refluxed appreciably. With phosphorus oxychloride present, however, the reaction mixture did not exhibit exothermicity.

The isolation of volatile dichlorocyclobutanones can usually be carried out by distillation from the reaction mixture, but purification of solid dichlorocyclobutanones sometimes presents a problem. This was especially evident in the trichloroacetyl bromide-activated zinc reactions of 2-cholestene (**6**) or indene. Crude products were sometimes dark viscous oils which were difficult to crystallize. With the trichloroacetyl chloride–phosphorus oxychloride method, however, crude products were much cleaner, usually being off-white solids.

With many reactive olefins like styrene or indene, it was sufficient to employ a 5% excess each of trichloroacetyl chloride and phosphorus oxychloride and a 10% excess of activated zinc. This is in contrast to literature[2] procedures for dichloroketene additions by either the dehalogenation or dehydrohalogenation method, in which a large excess of either olefin or acid chloride is usually employed. Product yields are significantly better in the presence of phosphorus oxychloride; for instance, the adduct of styrene was obtained in 87% yield, even though this olefin reportedly[2b] polymerizes in the presence of zinc salts.

Dichloroketene adducts of trisubstituted olefins were obtained in good yields (see Table I) and the dichloroketene adduct (**4**) of 2,3-dimethyl-2-butene was isolated in fair yield (41%). This example apparently represents the first successful addition of dichloroketene to a tetrasubstituted olefin. Thus the trichloroacetyl chloride–phosphorus oxychloride-activated zinc procedure seems to be the method of choice for the reaction of dichloroketene with unreactive olefins although a longer reaction time (15–20 h) is required.

However, the method was not applicable to enol ethers prone to polymerization by Lewis acids, namely dihydropyran and ethyl vinyl ether, and for the very reactive cyclopentadiene. With these olefins, only dark tars were isolated from the reaction mixtures. Also, the very electrophilic olefin acrylonitrile yielded no isolable cycloadduct.

Discussion

The role of the phosphorus oxychloride in the dichloroketene reactions appears to be that of complexing the $ZnCl_2$ produced in the reaction. In fact, $POCl_3$ is known[9] to form addition complexes with $ZnCl_2$ as well as with many Lewis acids, such as $AlCl_3$, BBr_3, $SnCl_4$, $TiCl_4$, although the nature of these addition compounds is rather unclear. It is not known whether the oxygen or the chlorine atom is donating electrons to the metal involved in the adduct. Since tertiary phosphine oxides in general are known to form complexes with acids and with Lewis acids,[9] we tried to substitute triphenylphosphine oxide for phosphorus oxychloride but it offered no advantages in these reactions. In fact $Ph_3P{=}O$ is much more expensive than phosphorus oxychloride, and it is difficult to remove. Again, no dichlorocyclobutanones could be isolated from the reactions of dihydropyran or cyclopentadiene.

In addition to triphenylphosphine oxide, dimethyl sulfoxide and pyridine *N*-oxide are known[10] to form complexes with acids. These compounds were not found useful in replacing phosphorus oxychloride in the dichloroketene reactions since they reacted with trichloroacetyl chloride and unreacted olefins were isolated. Also, thionyl chloride, phosphorus tribromide, and phosphorus pentachloride were found to have no beneficial effect in the dichloroketene cycloadditions.

That phosphorus oxychloride has no inherent stabilizing effect toward ketene was evidenced by the quantitative recovery of olefin **6** when dichloroketene was generated from dichloroacetyl chloride, triethylamine, in the presence of phosphorus oxychloride.

In summary, dichlorocyclobutanones derived from hindered or unreactive olefins can be obtained in good yield by dehalogenating trichloroacetyl chloride with activated zinc in the presence of the olefin and phosphorus oxychloride.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Infrared spectra were obtained of liquid films or carbon tetrachloride solutions as noted on a Perkin-Elmer 457 instrument. NMR spectra were recorded on a Varian A-60A or EM-360 spectrometer with Me_4Si as an internal standard. Mass spectra were determined on a Varian MAT CH5 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

Trichloroacetyl Chloride. This procedure is a slight modification of the literature procedure.[8]

To a stirred mixture of 97.0 g (0.59 mol) of Cl_3CCO_2H and 3.0 mL of DMF at 85 °C was added 51.0 mL (84.5 g, 0.71 mol) of thionyl chloride dropwise. When addition was complete, heating at this temperature was continued for 2 h. The bath temperature was lowered to 60–65 °C and the product distilled (40–45 °C at 20–25 mm) and collected in an ice-cooled receiver. The first few milliliters was discarded. The product was distilled one more time at reduced pressure and finally at atmospheric (625 mm) pressure (collected 180–110 °C) to yield 74.3 g (70%) of trichloroacetyl chloride.

Activation of Zinc. This procedure is a slight modification of the procedure of Brady.[2c] A stirred suspension of 10.0 g (0.15 m) of zinc dust in 40 mL of water was degassed by bubbling N_2 through it for 15 min. Then 750 mg (4.7 mmol) of $CuSO_4$ was added at once. The black suspension was stirred while N_2 was bubbled through it for an additional 45 min. The Zn–Cu couple was collected on a sintered glass funnel under a stream of N_2 and washed successively with 100 mL of degassed water and acetone. The Zn–Cu couple was transferred to a small flask under a stream of N_2 and dried at reduced pressure (0.2 mm) for 2 h. Nitrogen was admitted to the system when the vacuum was broken, and the Zn–Cu couple stored under N_2 in a tightly stoppered flask.

2,2-Dichloro-3-phenylcyclobutanone (1). The procedure for the addition of dichloroketene to styrene is illustrative: a 50-mL three-necked flask equipped with a condenser, addition funnel, magnetic stirrer, and N_2 inlet was flame dried while purged with N_2. When cool, the flask was charged with 1.1 mL (1.0 g, 9.6 mmol) of styrene, 0.69 g (10.5 mmol) of activated zinc, and 20 mL of anhydrous ether. The suspension was stirred under N_2 and a solution of 1.1 mL (1.83 g, 10.0 mmol) of Cl_3CCOCl and 0.92 mL (1.53 g, 10.0 mmol) of $POCl_3$ (distilled from K_2CO_3) in 10 mL of anhydrous ether was added dropwise over a 1-h period. When addition of the solution was complete, the mixture was refluxed with stirring for 2 h. The reaction mixture was then filtered through a pad of Celite and the unreacted zinc washed with 25 mL of ether. The ethereal solution was concentrated in vacuo to ca. 25% of its original volume, an equal volume of pentane added, and the solution stirred for a few minutes to precipitate the zinc salts. The solution was decanted from the residue, washed successively with water, a cold saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4, and the solvent was removed in vacuo to leave 1.93 g of crude **1**. Bulb-to-bulb distillation (oven 90 °C, 0.02 mm) afforded 1.80 g (87%) of **1**:[2b] IR (CCl_4) 1810 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 5 H), 4.18 (m, 1 H) and 3.56 (m, 2 H). The spectra of the crude and purified **1** were practically identical.

3,4-Benzo-6,6-dichlorobicyclo[3.2.0]hept-7-one (2). To a stirred mixture of 1.0 g (8.6 mmol) of indene and 0.62 g (9.5 mmol) of activated zinc in 25 mL of anhydrous ether was added a solution of 1.0 mL (1.65 g, 9.0 mmol) of Cl_3CCOCl and 0.83 mL (1.39 g, 9.0 mmol) of $POCl_3$ in 15 mL of anhydrous ether. After the solution was complete, the mixture was refluxed with stirring for 2 h. Workup afforded 1.78 g (92%) of a white solid which was purified by bulb-to-bulb distillation (oven 150 °C, 0.02 mm) to yield 1.57 g (81%) of **2**: IR (CCl_4) 1805 cm^{-1};[2d] NMR (CCl_4) δ 7.3 (m, 4 H), 4.50 (m, 2 H) and 3.3 (m, 2H). The spectra of crude and purified **2** were practically identical. When this reaction was repeated on a much larger scale (50 g of indene), the yield of purified **2** was slightly lower (71%).

4,4-Dichloro-*exo*-tricyclo[4.2.1.$0^{2,5}$]nonan-3-one (3). From 1.0 g (10.6 mmol) of norbornene, 0.76 g (11.7 mmol) of activated zinc in 30 mL of anhydrous ether, and addition of 1.22 mL (2.04 g, 11.2 mmol) of Cl_3CCOCl and 1.02 mL (1.72 g, 11.2 mmol) of $POCl_3$ in 15 mL of anhydrous ether, after 12 h of reflux, one obtained on bulb-to-bulb distillation (oven 120 °C, 0.02 mm) 1.15 g (70%) of **3**: IR (neat) 1802 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (m, 3 H), 2.75 (m, 3 H) and 1.95–0.95 (6 H).

2,2-Dichloro-3,3,4,4-tetramethylcyclobutanone (4). 2,3-Dimethyl-2-butene (1.0 g, 11.9 mmol), activated zinc (0.85 g, 13.0 mmol), Cl_3CCOCl (2.27 g, 12.5 mmol), $POCl_3$ (1.92 g, 12.5 mmol), after refluxing with stirring in 40 mL of anhydrous ether for 20 h, followed by bulb-to-bulb distillation (oven 120 °C, 0.02 mm), yielded 0.95 g (41%) of **4**: IR (CCl_4) 1795 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 6 H) and 1.27 (s, 6 H); *m/e* (%) no M+, 131 (1.5), 95 (3.1), 93 (1.1), 91 (2.3), 89 (6.4), 84 (18.4), 81 (5.6), 79 (6.6), 77 (5.6), 70 (100), 69 (16.2), 53 (11.5), 41 (39.0), 40 (26.7), and 38 (21.1).

Anal. Calcd for $C_8H_{12}Cl_2O$: C, 49.52; H, 6.20. Found: C, 49.23; H, 6.20.

8,8-Dichloro-1-methylbicyclo[4.2.0]octan-7-one (5). Following the procedure described for **1**, 1-methylcyclohexene (5.0 g, 52 mmol) and 3.7 g (57.2 mmol) of activated zinc in 100 mL of anhydrous ether was reacted with a solution of 6.0 mL (9.9 g, 54.6 mmol) of Cl_3CCOCl and 5.0 mL (8.37 g, 54.6 mmol) of $POCl_3$ in 50 mL of anhydrous ether. After 2 h of reflux and the usual workup, distillation afforded 8.5 g (79%) of **5**,[11] bp 62–63 °C (0.5 mm): IR (neat) 1800 cm^{-1}; NMR (CCl_4) δ 3.5 (broad, 1 H), 2.3–1.1 (8 H) and 1.5 (s, 3 H).

2a,2a-Dichloro-2α,3α-ethanocholestan-3a-one (7). To 10.0 g (27 mmol) of 2-cholestene[12] and 5.3 g (81 mmol) of activated zinc in 350 mL of anhydrous ether was added a solution of 5.9 mL (9.8 g, 54 mmol) of Cl_3CCOCl and 4.9 mL (8.2 g, 54 mmol) of $POCl_3$ in 50 mL of anhydrous ether. The mixture was refluxed with stirring for 15 h. The usual workup followed by recrystallization from ethyl formate yielded a first crop of 8.3 g and a second crop of 1.8 g (combined yield 78%) of **7**: IR (CCl_4) 1805 cm^{-1}; NMR (CCl_4) δ 4.2–3.6 (1 H) and 3.2–2.6 (1 H) as previously reported.[6]

2a,2a-Dichloro-2α,3α-ethano-2β-methylcholestan-3a-one (9). 2-Methyl-2-cholestene (8)[13] (2 g, 5.2 mmol) and 1.05 g (16 mmol) of activated zinc in 75 mL of anhydrous ether was refluxed with a solution of 1.14 mL (1.89 g, 10.4 mmol) of Cl_3CCOCl and 0.95 mL (1.59 g, 10.4 mmol) of $POCl_3$ in 35 mL of anhydrous ether. TLC (silica gel, pentane/benzene (3:1) eluent) indicated that olefin was consumed after 20 h. The usual workup afforded 2.50 g (97%) of a yellow solid. Recrystallization from ethyl formate–methanol gave 1.85 g (72%) of **9**, mp 128–129 °C: IR (CCl_4) 1800 cm^{-1}; CD ($CHCl_3$); NMR ($CDCl_3$) δ 3.60–3.33 (1 H) and 1.50 (2β-methyl); MS *m/e* (%) M + 2 496 (15.0), M+ 494 (21.0), 468 (18.8), 466 (27.1), 383 (21.2), 329 (37.9), 287 (30.7), 119 (34.0), 107 (43.5), 95 (69.0), 105 (35.6), 81 (58.8), and 42 (100).

Anal. Calcd for $C_{30}H_{48}Cl_2O$: C, 72.70; H, 9.76. Found: C, 72.93; H, 9.88.

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Registry No.—Cl_3CCO_2H, 76-03-9; Cl_3CCOCl, 76-02-8; $Cl_2C{=}C{=}O$, 4591-28-0; $POCl_3$, 10025-87-3.

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Electrochemical Acetoxylation of *N*-Acetylindolines and *N*-Acetylindoles. A New Synthesis of Indigos

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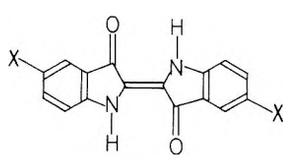
Electrochemical acetoxylation of *N*-acetylindolines **3** in AcOH–Et_3N at potentials 1.1–1.7 V vs. SCE, 4 faradays/mol of electricity, using platinum electrodes afforded the corresponding 2,3-diacetoxyindolines **5** in 70–77% yields. Likewise, *N*-acetylindoles **4** gave **5** in 76–82% yields. The acetate **5** could also be prepared from indoline (**2**) without isolating the intermediates **3** and **4**. Thermal decomposition of **5** at 140–145 °C gave *N*-acetylindoxyl acetates **7** in 81–87% yields and subsequent hydrolysis with 1 M aqueous sodium hydroxide provided indigos in 86–96% yields. Electrochemical bromination of **3a** (X = H) using various alkali bromides led to the corresponding bromide **3b** (X = Br) in 95–99% yields, which can be used as a precursor of bromoindigo synthesis.

Recent revival in the use of indigo dyes has stimulated new synthetic interest. Instead of the well-known preparative methods involving alkali fusion of phenylglycine[1] or phenylglycine-*o*-carboxylic acid,[2] we have examined the possibility of using an electrochemical reaction as a nonpolluting procedure for preparing indigos.[3]

We described herein electrochemical acetoxylation of *N*-acetylindolines **3** and *N*-acetylindoles **4** leading to the corresponding 2,3-diacetoxyindolines **5** as well as two-step conversion of the diacetates **5** into indigos **1** via *N*-acetylindoxyl



1a X=H
b X=Br

acetates **7** and also the electrochemical bromination of **3a** (X = H) leading to **3b** (X = Br) as a precursor of bromoindigo synthesis. Actually, we have succeeded in obtaining **5** directly from **2** without isolating **3** and **4** in a one-batch procedure.

A reverse synthetic pathway from indigos **1** to indoline (**2**) via the key intermediate **5** is outlined in Scheme I. Here, it can be seen that our novel indigo synthesis consists of three steps starting from either **2, 3,** or **4** via the intermediates **5** and **7.** Electrolysis of **3a** (X = H) in AcOH–Et_3N at potentials 1.1–1.7 V vs. SCE, applied voltages 2.0–2.9 V, current densities 3.3 mA/cm^2, using platinum foil electrodes consumed ca. 4 faradays/mol of electricity (over 80% of current efficiency) for 3 h (Table I, entry 1). All three products, 1-acetyl-2,3-diacetoxyindoline (**5a,** X = H, 77%), **4a** (X = H, 3%), and 1-acetylindoxyl acetate (**7a,** X = H, 2%) were separable and were

Scheme I

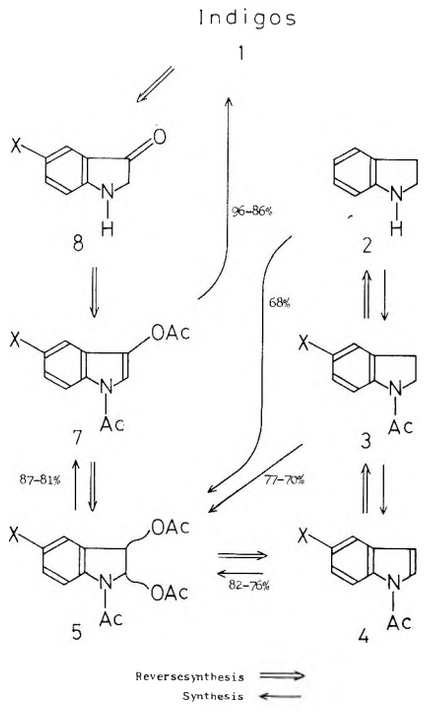


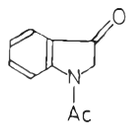
Table I. Conditions[a] and Results of Electrochemical Acetoxylation of *N*-Acetylindolines (3) and *N*-Acetylindoles (4)

Entry	Substrate (0.62 mmol)	Registry no.	Solvent AcOH, mL	Supporting electrolyte (mL)	Current density, mA/cm²	Quantity of electricity, faradays /mol	Product yields,[b] % 4	5	6	7	Recovered 3
1	**3a**	16078-30-1	9	Et_3N (1)	3.3	4.0	3	77		2	
2	**3a**		9	Et_3N (1)	1.8–0.1[c]	0.9	22				64
3	**4a**	576-15-8	9	Et_3N (1)	1.7	2.0	3	82		2	
4	**3a**		9.5	DBU (0.5)	6.7	4.5	3	77		2	
5	**3a**		9	Pyridine (1)	6.7	5.0	1	70		2	
6	**3a**		9	Et_2NH (1)	6.7	5.0	2	61		1	5
7	**3a**		9	Piperidine (1)	6.7	5.0	2	53		1	6
8	**3a**		9	Cyclohexylamine (1)	6.7	5.0	3	49		2	3
9	**3a**		10	$AcONH_4$ (250)[d]	1.7	3.0	6	48		5	10
10	**3a**		10/0.2[e]	Et_4NClO_4 (100)[d]	1.7	3.0					74
11	**3a**		8	Et_4NOTs (100)[d]	1.7–1.0	2.0					90
12	**3a**		10/0.5[e]	AcONa–Et_4NClO_4(100/100)[d]	3.3	3.0	1	2	20		26
13	**3a**		8/1[e]	Et_3N (1)	3.3	4.0	4	8	48		10
14	**3b**	22190-38-1	9	Et_3N (1)	3.3	4.0	7	70			
15	**4b**	61995-52-6	9	Et_3N (1)	3.3	2.0	4	76			
16	**3b**		8/1[e]	Et_3N (1)	5.0	4.5	10	5	51		

[a] The electrolyses were carried out at 22–28 °C, Pt, 3 cm². [b] Isolated yields. [c] Under controlled potential at 1.4 V vs. SCE. [d] The quantity is shown in mg scale. [e] Milliliter of water mixed in the solvent.

characterized. One-batch electrosynthesis of **5a** from **2** could be achieved on treatment with acetic anhydride–acetic acid upon heating for 2 h before the electrolysis.

The voltammetric results (Figure 1) from the electrolysis of **3a** reveal that the electrolytic oxidation of **3a** at 1.1–1.4 V vs. SCE would provide **4a** preferably, however, the competitive electrolysis of **4a** would proceed at 1.4–1.7 V vs. SCE, giving **5a**. Actually, the controlled potential electrolysis of **3a** at 1.4 V vs. SCE at the current from 1.8 to 0.13 mA/cm², 0.9 faraday/mol of electricity, for 9.5 h afforded **4a** (22%, current efficiency 49%) as well as the recovered **3a** (64%) (entry 2). In the same electrolytic conditions as given in entry 1, conversion of **4a** into **5a** could be carried out smoothly in 82% yield along with the formation of **7a** (2%) after passing 2 faradays/mol of electricity (entry 3). The minor product **7a** is expected to arise from the elimination of acetic acid from **5a**. The complete conversion of **5a** to **7a** was accomplished in 87% yield by heating **5a** at 140–145 °C for 5 h. However, 1-acetylindoxyl (**9**) was obtained in 71% yield, when a benzene solution of **5a**



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was refluxed for 10 h in the presence of potassium hydrogen sulfate.

The electrolytic acetoxylation of **3a** using various tertiary amines as a supporting electrolyte shows that triethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), and pyridine are a surprisingly effective supporting electrolyte in acetic acid, giving 77–70% yields of **5a** (entries 1, 4, and 5). Secondary and primary amines, including diethylamine, piperidine, and cyclohexylamine, and ammonium acetate were less effective and furnished **5a** in 61–48% yields (entries 6, 7, 8, and 9). In contrast, tetraethylammonium perchlorate and/or tosylate was completely ineffective as a supporting electrolyte in the medium (entires 10 and 11), since no detectable amount of **5a** was found in the electrolysis products. The results demonstrate apparent discrepancy in comparison with the Eberson's investigation, indicating that the side-chain acetoxylation does not require the presence of acetate ion, whereas nuclear acetoxylation cannot be achieved in the absence of acetate ion.[4] Since the side-chain acetoxylation products have been obtained in the media such as AcOH–$NaClO_4$ and/or AcOH–Et_4NOTs, it will be also noted that in the electrolysis of **3a** in the presence of acetate ion (entries 1, 2, 4–9) absence of nuclear acetoxylation products distinguishes the reported assumption. However, complex products including nuclear methoxylation derivatives were obtained, when **3a** was electrolyzed in MeOH–Et_4NClO_4. On the other hand, electrolysis of **2** in MeOH–Et_4NClO_4 afforded the dimeric product **10**[5] in 40–50% yield as a major product. The electrolysis of **2** without protecting the secondary amino group in AcOH–Et_3N did not yield **5a** but provided a film on the anode.[6]

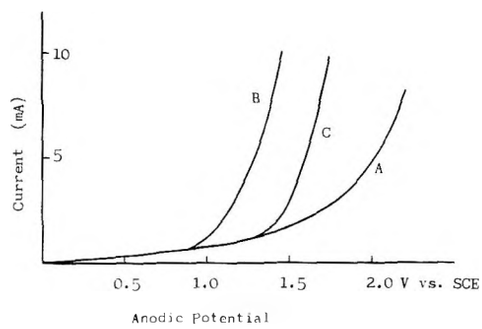
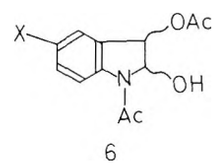


Figure 1. Current–potential curves: (A) Et_3N–AcOH (1:9) solution; (B) in the presence of 0.06 M of *N*-acetylindoline (**3a**); (C) in the presence of 0.06 M of *N*-acetylindole (**4a**), Pt electrodes, at 20 °C.

Use of acetic acid containing a small amount of water with triethylamine or AcONa–Et_4NClO_4 as an electrolyte led to the formation of **6a** (X = H, 20–48%) as a major product along with minor products **4a** (1–4%) and **5a** (2–8%) (entries 12 and



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13). Treatment of the monoacetate **6a** with acetic anhydride–pyridine at 40 °C for 2 h afforded **5a** smoothly.

In view of both the comparison of ^1H NMR spectra of **6a**

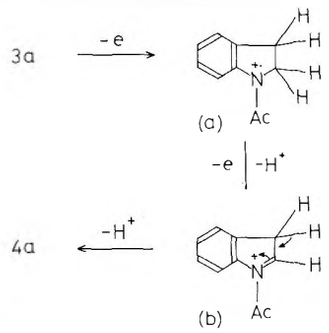
Table II. Electrochemical Bromination of *N*-Acetylindoline (3a) with Various Bromides in Aqueous 93% AcOH[a]

Entry	Supporting electrolyte (mg)	Current density mA/cm^2	Quantity of electricity, faradays/mol	Product yield, %[b] of **3b**
17	NH_4Br (100)	5.0–2.7	2.2	96
18	LiBr (81)	3.8–2.0	2.0	98
19	NaBr (100)	2.7–1.7	2.2	95
20	KBr (120)	3.8–2.7	2.7	99
21	$MgBr_2 \cdot 6H_2O$ (234)	2.0–1.5	2.0	99

[a] A solution of **3a** (100 mg) in aqueous 93% AcOH (10 mL) was electrolyzed at 22–25 °C at 3 V (applied voltage), Pt, 3 cm^2. [b] Isolated yields.

with **5a** and thermal dehydration of **6a**, affording **7a**, there must be present a hydroxy group at the C(2) position of **6a**. This assumption is confirmed by a chemical shift of the C(2) proton at δ 5.60 in the ^{1}H NMR spectrum of **6a** and one at δ 6.64 in the spectrum of **5a**. In this connection, the ^{1}H NMR spectra of **5a** and **6a** have signals as a singlet at δ 5.88 and 5.87 due to every C(3) proton

A reasonable explanation for the electrochemical acetoxylation of **3a** leading to **5a** involves the formation of *N*-acetylindole (**4a**). The formation of **4a** from **3a** can be explained in terms of the mechanism suggested by Mann and his coworkers[7] for the anodic oxidation of aliphatic amines at platinum electrodes in acetonitrile. This mechanism leads to a cation radical intermediate (a), after **3a** undergoes one-



electron discharge on the anode, which suffers from further one-electron oxidation followed with deprotonation to produce the cation intermediate (b) as a precursor of **4a**. It will be noted that highly basic amines, i.e., triethylamine, DBU, and pyridine, all of which have a tertiary nitrogen atom, would assist the elimination of hydrogen atom at the C(3) carbon of **3a**. The electrochemical conversion of **4a** to **5a** would proceed in a similar fashion to the electrolytic acetoxylation of 3-alkylindene, giving the corresponding 1,2-diacetoxyindane.[8]

Efficient electrobromination of **3a** with various bromides was carried out under several conditions and the yields of **3b** are shown in Table II. Otherwise, the chemical bromination of **3a** with bromine in acetic acid has been shown to give **3b** in 85% yield.[9] Electrolysis of **3a** with ammonium bromide in aqueous 93% acetic acid at the potential between 0.8 and 0.9 V vs. SCE, an applied voltage 3 V, current densities 3–5 mA/cm^2, consumed ca. 2.2 faradays/mol of electricity (87% of current efficiency), giving **3b** (96%) (entry 17). Change of bromides did not affect the excellent yield of the formation of **3b** (entries 18–21).

In considering the formation of **3b** from **3a** at 0.8–0.9 V vs. SCE, a cationic species of **3a** on the aromatic ring is unlikely due to the lower oxidation potential of ammonium bromide (Figure 2) in comparison with that of **3a** (anodic limit ca. 1.0 V). The treatment of **3a** with a bromine solution, prepared

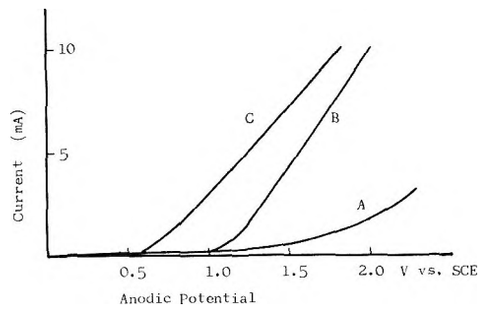


Figure 2. Current–potential curves: (A) 0.13 M $LiClO_4$ aqueous 93% AcOH: (B) in the presence of 0.06 M *N* acetylindoline (**3a**); (C) 0.1 M NH_4Br aqueous 93% AcOH (Pt electrodes, at 20 °C).

previously by electrolysis of AcOH–NH_4Br with 2 faradays/mol of electricity (based on **3a**), afforded **3b** in 25% yield. The inferior result from the chemical bromination in the same medium may be accounted for by considering lack of some contribution from the electrode process. A mechanistic explanation for this reaction would be provided by the assumption based on the aromatic–bromine charge transfer complex[10] and/or the absorption of bromine atoms at the surface of the platinum electrodes.[11]

Subsequent electrolytic acetoxylation of **3b** was performed under a constant current of 3.3 mA/cm^2, applied voltages of 2.1–3.1 V, ca. 4 faradays/mol, at 22–23 °C, giving **5b** in 70% yield as well as **4b** (7%) (Table I entry 14). Likewise, electrolysis of **4b** prepared by dehydrogenation[12] of **3b** afforded **5b** in 76% yield (entry 15). In wet AcOH–Et_3N, electrolysis of **3b** afforded **6b** (X = Br, 51%) as well as **4b** (10%) and **5b** (5%) (entry 16). This diacetate **5b**, when heated to 135–145 °C for 5 h under diminished pressure, decomposed to give **7b**[13] (81%).

Indigo and 5,5′-dibromoindigo (**1a** and **1b**[14]) were obtained in 86–96% yields, respectively, after the indoxyl acetates **7a** and **7b** were hydrolyzed by aqueous 1 M sodium hydroxide at 60–65 °C under exposure to atmosphere. Similarly, base-catalyzed hydrolysis of **9** also gave **1a** in excellent yield.[15a] The direct transformation of **7** into **1** would be considered to undergo oxidative coupling[15] of **8** and/or **9** by the aid of oxygen after the alkaline hydrolysis.

Experimental Section

All melting and boiling points were uncorrected. IR spectra were recorded on a JASCO model IRA-1 spectrometer. ^{1}H NMR spectra were obtained with a Hitachi R-24 spectrometer. Mass spectral analyses were carried out on a JEOL JMS D-100 spectrometer at 75 eV. Current–potential measurements were performed by using Kowa Electronics models PGS-1550 potentio-galvanostat and FG-102A function generator. Column chromatography was carried out using Wako gel C-200 (silica gel) with benzene–AcOEt as an eluent.

Materials. Commercially available indoline (**2**), AcOH, and Et_3N were distilled under reduced pressure before use. *N*-Acetylindoline (**3a**) was obtained on treatment of **2** with Ac_2O in the presence of pyridine.[16] *N*-Acetylindole (**4a**) was prepared from **3a** according to the reported procedure.[12]

Electrolysis Apparatus. An undivided cell was equipped with two platinum foil electrodes (3 cm^2, 5 mm apart), a gas lead pipe, and a thermometer. The vessel was immersed in a water bath at 22–25 °C.

1-Acetyl-2,3-diacetoxyindoline (5a) from 3a. A mixture of **3a** (100 mg, 0.62 mmol) and Et_3N (1 mL) in AcOH (9 mL) was electrolyzed under a constant current (3.3 mA/cm^2) at applied voltages of 2.0–2.9 V, 1.1–1.7 V vs. SCE at 23–25 °C. After 4 faradays/mol of electricity were passed, the solvent was evaporated. The solution concentrated was taken up in benzene–AcOEt (10:1) and washed with aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). After removal of most of the solvent, the residue was chromatographed (SiO_2, benzene–AcOEt 20:1) to give three fractions: The first eluent contained 3 mg of **4a** (3%): bp 115–118 °C (5 mm) (lit.[17] bp 152–153 °C (14 mm)); IR (neat) 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3, AcN), 6.57

(d, 1, J = 4 Hz, HC=CN), 7.05–7.60 (m, 4, ArH, C=CHN), 8.25–8.55 (m, 1, ArH). The second fraction consisted of 3 mg of **7a** (2%): mp 81 °C (lit.[13] mp 82 °C); IR (Nujol) 1745 (C=O), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.33 (s, 3, AcO), 2.55 (s, 3, AcN), 7.18–7.62 (m, 3, ArH), 7.63 (s, 1, C=CHN), 8.30–8.47 (m, 1, ArH). The third run involved 132 mg of **5a** (77%, trans/cis 9:1 evaluated by ^1H NMR integration). The trans isomer of **5a** was isolated by careful column chromatography (SiO_2, benzene–AcOEt 30:1) as first coming fraction, white crystals, mp 126 °C (cyclohexane): IR (Nujol) 1735 (C=O), 1682 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3, AcO), 2.11 (s, 3, AcO), 2.30 (s, 3, AcN), 5.94 (s, 1, HCCN), 6.71 (s, 1, HCN), 6.95–7.65 (m, 3, ArH), 7.95–8.20 (m, 1, ArH); mass spectrum m/e (rel intensity) 277 (M^+, 23), 235 (10), 176 (17), 175 (32), 133 (100), 123 (23), 117 (17), 93 (12), 77 (13). Anal. Calcd for $C_{14}H_{15}O_5N$: C, 60.63; H, 5.45. Found: C, 60.78; H, 5.39.

In a similar manner, the electrolysis of **3b** (3.3 mA/cm^2, 2.1–3.1 V, 4.0 faradays/mol, 22–23 °C) gave **1-acetyl-5-bromo-2,3-diacetoxyindoline (5b,** 70%) together with 1-acetyl-5-bromoindole (**4b,** 7%). The diacetate **5b:** mp 112 °C (cyclohexane); IR (Nujol) 1745 (C=O), 1690 cm^{-2} (C=O); ^1H NMR ($CDCl_3$) δ 2.11 (s, 3, AcO), 2.14 (s, 3, AcO), 2.30 (s, 3, AcN), 5.90 (s, 1, HCCN), 6.70 (s, 1, CHN), 7.30–7.70 (m, 2, ArH), 8.05 (d, 1, J = 9 Hz, ArH); mass spectrum m/e (rel intensity) 357 (M^+ + 2, 5), 355 (M^+, 5), 315 (5), 255 (22), 253 (21), 213 (46), 211 (48), 43 (100). Anal. Calcd for $C_{14}H_{14}BrNO_5$: C, 47.21; H, 3.96. Found: C, 47.17; H, 4.14.

The 5-bromoindole **4b:** mp 109 °C (hexane-benzene 5:1); IR (Nujol) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.58 (s, 3, Ac), 6.54 (d, 1, J = 4 Hz, HC=CN), 7.25–7.55 (m, 2, C=CHN, ArH), 7.65 (d, 1, J = 2 Hz, ArH), 8.30 (d, 1, J = 8 Hz, ArH). Anal. Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.36. Found: C, 50.44; H, 3.53.

One-Batch Synthesis of 5a from 2 To a mixture of Ac_2O (210 mg, 2.06 mmol), AcOH (18 mL), and Et_3N (2 mL) was added indoline (**2**) (238 mg, 2.00 mmol). After being stirred at 35–40 °C for 2 h, the solution was allowed to cool to 20 °C and electrolyzed under the same conditions as described above and worked up. The residue was chromatographed (SiO_2, benzene–AcOEt 20:1) to give **5a** (68%) as well as minor products **4a** (5%) and **7a** (8%).

Electrolytic Acetoxylation of 4a. A mixture of **4a** (100 mg, 0.63 mmol), AcOH (9 mL), and Et_3N (1 mL) was electrolyzed under a constant current (1.7 mA/cm^2), at applied voltages of 1.9–3.0 V, 1.4–1.7 V vs. SCE at 26–27 °C. After passing 2 faradays/mol of electricity (7 h), the mixture was concentrated. The residue was worked up in the usual manner and chromatographed (SiO_2, benzene–AcOEt 20:1) to give **5a** (82%) along with **4a** (3%) and **7a**[13] (2%).

Similarly, the electrolysis of **4b** (2 faradays/mol, 3.3 mA/cm^2, 2.3–3.4 V, 22–23 °C) gave **5b** (76%) and **4b** (4%).

1-Acetylindoxyl Acetate (7a). The trans isomer of **5a** (100 mg, 0.36 mmol) was heated to 140–145 °C under reduced pressure (20–25 mm) for 5 h and then the mixture was chromatographed (SiO_2, benzene) to give **7a** (67 mg, 87%): mp 81 °C (lit.[13] mp 82 °C); IR (Nujol) 1740 (C=O), 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3, AcO), 2.56 (s, 3, AcN), 7.15–7.65 (m, 3, ArH), 7.71 (s, 1, C=CHN), 8.30–8.60 (m, 1, ArH).

In a similar manner, the thermal deacetoxylation of **5b** gave **1-acetyl-5-bromoindoxyl acetate (7b)** in 81% yield: mp 122–123 °C (hexane–benzene 5:1) (lit.[13] mp 124 °C); IR (Nujol) 1760 (C=O), 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.37 (s, 3, AcO), 2.58 (s, 3, AcN), 7.30–7.75 (m, 3, ArH, C=CHN), 8.30 (d, J = 9 Hz, ArH).

3-Acetoxy-1-acetyl-2-hydroxyindoline (6a). A mixture of **3a** (100 mg, 0.62 mmol), AcOH (8 mL), Et_3N (1 mL), and H_2O (1 mL) was electrolyzed under a constant current (3.3 mA/cm^2) at 24–26 °C. After 4 faradays/mol of electricity were passed, the solution was worked up in the usual manner to give **6a** (48%) as well as four minor products **3a** (10%), **4a** (4%), and the cis and trans isomers **5a** (8%). The hydroxyindoline **6a,** white crystals: mp 142 °C (benzene); IR (Nujol) 3200 (OH), 1740 (C=O), 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3, AcO), 2.35 (s, 3, AcN), 4.70 (b, 1, OH), 5.60 (b, 1, HCN), 5.87 (s, 1, HCAr), 6.85–7.60 (m, 3, ArH), 7.80–8.25 (m, 1, ArH); mass spectrum m/e (rel intensity) 235 (M^+, 35), 193 (19), 175 (24), 162 (8), 150 (23), 133 (100), 122 (99), 105 (19), 104 (21), 94 (20), 93 (19), 78 (13), 77 (27), 51 (12), 43 (96). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57. Found: C, 61.43; H, 5.70.

3-Acetoxy-1-acetyl-5-bromo-2-hydroxyindoline (6b). The electrolysis of **3b** in AcOH–Et_3N–H_2O (8:1:1) (5.0 mA/cm^2, 2.2–2.3 V, 4.5 faradays/mol, 24–25 °C) gave **6b** in 51% yield together with **4b** (10%) and **5b** (5%). The acetate **6b,** white crystals: mp 136 °C (benzene); IR (Nujol) 3160 (OH), 1730 (C=O), 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3, AcO), 2.36 (s, 3, AcN), 4.75 (b, 1, OH), 5.65 (b, 1, HCN), 5.87 (s, 1, HCAr), 7.30–7.60 (m, 2, ArH), 7.75–8.15 (m, 1, ArH); mass spectrum m/e (rel intensity) 315 (M^+ + 2, 19), 313 (M^+, 17), 273 (18), 271 (15), 255 (6), 242 (7), 213 (31), 211 (32), 202 (23), 200 (28), 133 (20), 45 (21), 43 (100), 41 (23). Anal. Calcd for $C_{12}H_{12}BrNO_4$: C, 45.88; H, 3.85. Found: C, 45.77; H, 3.93.

Acetylation of 6a. A solution of **6a** (30 mg, 0.13 mmol) in Ac_2O (1 mL) and pyridine (1 mL) was stirred for 2 h at 40 °C. After removal of most of the solvents, the residue was diluted with water and extracted with benzene–AcOEt (10:1). Usual work-up followed by chromatography (SiO_2, benzene–AcOEt 20:1) gave **5a** (93%).

1-Acetylindoxyl (9). A mixture of **5a** (80 mg, 0.29 mmol) and $KHSO_4$ (400 mg) in benzene (5 mL) was refluxed for 10 h. Removal of the solvent followed by column chromatography (SiO_2, benzene–AcOEt 10:1) gave **9** (39 mg, 71%): mp 133–134 °C (EtOH–H_2O 3:1) (lit.[13] mp 138 °C); IR (Nujol) 1720 (C=O), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.33 (s, 3, Ac), 4.30 (s, 2, CH_2N), 7.00–7.75 (m, 3, ArH), 8.30–8.60 (b, 1, ArH).

Electrolytic Bromination of 3a. A solution of **3a** (100 mg, 0.62 mmol) and NH_4Br (100 mg, 1.02 mmol) in aqueous 93% AcOH (10 mL) was electrolyzed under a constant applied voltage of 3 V, 0.8–0.9 V vs. SCE, 5–3 mA/cm^2, at 23–24 °C. After 2.2 faradays/mol of electricity was passed, the solvent was evaporated under reduced pressure. The residue was taken up in benzene, washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2, benzene–AcOEt 10:1) to give 1-acetyl-5-bromoindoline (**3b**) (146 mg, 96%) as white crystals: mp 118 °C (MeOH) (lit.[9] mp 118–119 °C); IR (Nujol) 1653 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3, Ac), 3.07 (t, 2, J = 9 Hz, CH_2Ar), 3.99 (t, 2, J = 9 Hz, CH_2N), 7.00–7.40 (m, 2, ArH), 8.05 (d, 1, J = 9 Hz, ArH). The yields of **3b** using various bromides are shown in Table II.

Indigo (1a) was obtained on treatment of **7a** (120 mg, 0.55 mmol) with aqueous 1 M NaOH (10 mL) at 60–65 °C for 5 h. The indigo-blue solution was acidified to pH 6 with aqueous 5% HCl and the blue solid material was filtered off and washed with water. After drying, there was obtained 67 mg (96%) of **1a,** whose spectral data were identical with those of authentic sample.

Similarly, 5,5′-dibromoindigo (**1b**) was obtained from **7b** in 86% yield.

Registry No.—**1a,** 482-89-3; **1b,** 84-40-2; *cis*-**5a,** 66358-39-2; *trans*-**5a,** 66358-40-5; **5b,** 66358-41-6; **6a,** 66358-42-7; **6b,** 66358-43-8; **7a,** 16800-67-2; **7b,** 33588-54-4; **9,** 16800-68-3; **10,** 66358-44-9.

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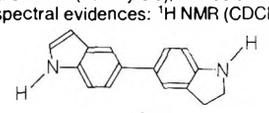
(5) The electrolysis of **2** in MeOH–Et_4NClO_4 at an applied voltage of 3 V (7–1 mA/cm^2) with Pt electrodes, after passing 2 faradays/mol of electricity, afforded a green material **10** (48% yield), whose structure was tentatively assigned from the spectral evidences: ^1H NMR ($CDCl_3$) δ 3.04 (t, 2, J = 8 Hz, CH_2Ar), 3.86 (t, 2, J = 8 Hz, CH_2N), 6.30–8.10 (m, 10, ArH, HC=CH, HN). The dimeric product **10,** however, underwent breakdown to the reddish complex on standing for several hours.



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(14) 5,5′-Dibromoindigo (**1b**) has been synthesized by both chemical and electrochemical brominations of **1a** in heterogenious media: (a) E. Grandmouzin, *Ber.*, **42,** 4408 (1909); (b) Fr. Fichter and F. Cueni, *Helv. Chim. Acta*, **14,** 651 (1931).
(15) (a) D. Vorlander and J. Pfeiffer, *Ber.*, **52,** 325 (1919); (b) G. A. Russell and G. Kaupp, *J. Am. Chem. Soc.*, **91,** 3851 (1969).
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Reaction of *o*-Phthalaldehyde and Thiols with Primary Amines: Formation of 1-Alkyl(and aryl)thio-2-alkylisoindoles

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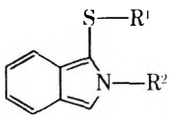
The fluorogenic reaction of *o*-phthalaldehyde (OPTA) and β-mercaptoethanol (MERC) with primary amino acids gives a 1-alkylthio-2-alkylisoindole as the product. The structure of this group of previously unknown isoindoles was determined (1) from an in situ analysis of the adducts formed in solution from OPTA, MERC or ethanethiol (ET), and *n*-propylamine, (2) from the characterization of solid derivatives of these MERC and ET adducts, and (3) from the studies of two isolable isoindoles (an OPTA/*tert*-butylthiol/*n*-propylamine adduct and a dimeric adduct formed from OPTA, ethanedithiol, and *n*-propylamine). The reaction is found to be quite general as OPTA and numerous thiols rapidly react with *n*-propylamine or leucine to give isoindoles in excellent yield. Most adducts were not isolated, but their physical properties in solution were qualitatively identical with those of the *tert*-butyl and dimeric ethanedithiol adducts. Analyses of the chemical shifts of the isoindole alkyl substituents in the NMR spectra support the previous conclusions that these heterocycles have relatively low levels of aromatic character. The addition sequence of the reaction is important; the best results are obtained by mixing OPTA and thiol before adding the amine. With some thiols, this procedure results in the initial formation of a 1-alkylthio-3-hydroxy-1,3-dihydroisobenzofuran. However, these 1:1 adducts do not appear to be obligatory intermediates in the subsequent reaction with primary amines to form 1-thio-substituted isoindoles.

The fluorogenic reaction of *o*-phthalaldehyde (OPTA) and β-mercaptoethanol (MERC) with amines[1,2] and amino acids and proteins[3-9] has recently attracted much attention due to the high sensitivity of the assay which can be conducted in aqueous solutions. Thus, picomole quantities of amino acids can be readily detected. In recent preliminary communications we deduced that these intensely fluorescent OPTA reaction products are 1-alkylthio-2-alkyl-substituted isoindoles **1**.[2,10]



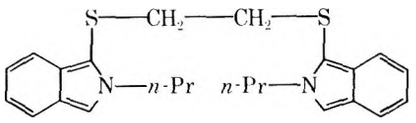
1. R^1 = alkyl or aryl; R^2 = alkyl

Isoindoles in general are quite reactive and eluded isolation until 1951.[11,12] In spite of their 10-π-electron apparently aromatic structure, N-substitution and especially halogen substitution[13-15] are required to increase the stability of isoindoles not conjugated with other unsaturated functional groups. Very few oxygen-[13,16] or nitrogen-substituted[17] isoindoles have been reported, and the effect of such substitution on isoindole stability is not yet clear. For this reason, thio-substituted isoindoles **1** are an important new class of hetero-substituted isoindoles which should be useful in further defining the physical and chemical properties of these interesting 10-π-electron bicyclic heterocycles. In this paper we present the details of our preliminary communications,[2,10] describe the preparation and physical properties of several new 1-alkyl(and aryl)thio-2-alkylisoindoles, and assess the scope and mechanism of the OPTA reaction. A discussion of the fluorescence properties of these compounds can be found elsewhere.[18]

Results and Discussion

1-(*tert*-Butylthio)-2-*n*-propylisoindole. In a modification of our earlier procedure,[10] addition of 1 equiv of *n*-propylamine to an equal molar amount of OPTA and *tert*-butylthiol caused an exothermic reaction, after which **1** (R^1 = *t*-Bu, R^2 = *n*-Pr) soon crystallized out of solution in 86% yield. After recrystallization this material was identical with the previously characterized *tert*-butyl adduct.[10] An analytical sample remelted with very little change in the melting point, and it could be stored at −20 °C for six months. In solution this isoindole was less stable, and complete destruction of the adduct (5×10^{-3} M in isooctane) occurs after <40 h of exposure to room lighting. Thus, this *tert*-butyl adduct still possesses the high reactivity characteristic of simple isoindoles.

Ethanedithiol Dimer Adduct 2. Analytically pure **2**



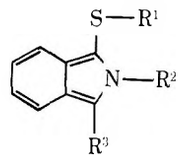
2

crystallized out of a reaction solution of 0.5 equiv of ethanedithiol and 1 equiv each of OPTA and *n*-propylamine in nearly quantitative yield. While the solid adduct is reasonably stable in air at room temperature, it is discolored by room light and decomposes in solution. Rapid, low temperature, light-shielded recrystallizations consistently gave less pure solids. Thus, like the *tert*-butyl adduct, the isoindole **2** is only relatively more stable than other simple isoindoles.

β-Mercaptoethanol and Ethanethiol Adducts. As was reported earlier,[2,19] neither of these adducts was readily isolable. However, as seen for the *tert*-butyl and dimeric ethanedithiol adducts directly, NMR and TLC analyses of the reaction solutions revealed that the MERC and ET adducts could be formed in >90% yield and purity. Thus, the inability to isolate these latter adducts did not preclude their characterization. The IR spectra of these adducts and the *tert*-butyl and ethanedithiol dimer adducts each display numerous prominent bands that are undoubtedly characteristic of this isoindole ring system. Several of these bands (i.e., those at 3030, ~2900, 1460, and ~746 cm^{-1}) and the lack of aromatic bands in the region of 1600–1500 cm^{-1} have also been observed in the IR spectrum of isoindole itself.[20] Likewise, the MERC, ET, *tert*-butyl, and ethanedithiol dimer adducts have virtually superimposable UV spectra (Table I).

The ^1H NMR spectra of the MERC,[2] ET, *tert*-butyl, and ethanedithiol dimer adducts are almost identical (Table II) and thus, with the above compared UV data, firmly establish the isoindole ring structure for the unisolated MERC and ET adducts. Theoretical[21] and experimental ^1H NMR spectra of isoindole[14,20] and a detailed analysis of the spectrum of *N*-methylisoindole[22] give a pattern and assignment[21,22] of the aromatic region protons similar to that of these adducts. A

Table I. Effect of Substituents and Solvents on the UV Spectral Properties of Isoindoles 1[a]

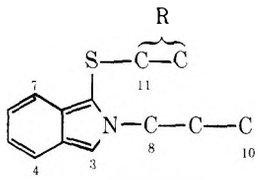


1

				95% EtOH			Isooctane		
R^1	R^2	R^3	Registry no.	λ_{max} (nm)	$\lambda_{shoulder}$ (nm)	$\epsilon \times 10^{-3}$	λ_{max} (nm)	$\lambda_{shoulder}$ (nm)	$\epsilon \times 10^{-3}$
Et	*n*-Pr	H	61214-22-0	333	~345	7.5	331, 346	~318	8.5
$-CH_2CH_2OH$	*n*-Pr	H	61214-21-9	332	~345	7.6	330, 345	~317	8.4
t-Bu	*n*-Pr	H	64807-91-6				333, 348	~320	9.3
Ph	*n*-Pr	H	66161-39-5	330	~343	7.1			
$-CH_2COOMe$	*n*-Pr	H	66161-40-8	332	~345	8.6			
$-CH_2CH_2SH$	*n*-Pr	H	66161-41-9	332	~345	7.4			
$-CH_2\rightarrow_2$	*n*-Pr	H	66161-42-0	333	~346	14.4			
$-CH_2CHOHCH-OHCH_2SH$	*n*-Pr	H	66161-43-1	333	~345	7.1			
$-CH_2CHOH\rightarrow_2$	*n*-Pr	H	66161-44-2	332	~345	14.4			
t-Bu	*n*-Pr	-S-*t*-Bu	66161-45-3				344, 361	~330	17.0
$-CH_2CH_2OH$	-CH(*i*-Bu)COOH	H	66161-46-4	336	~350	5.7			

[a] All adducts were formed as described in the Experimental Section. The solid adducts were diluted directly into isooctane (for the two *tert*-butyl adducts) or dissolved in EtOAc and then diluted 1:400 with 95% EtOH (for the ethanedithiol dimer). The MERC and ET adducts formed in 95% EtOH were diluted 1:333 with isooctane or 95% EtOH. All other solutions containing the initially formed adducts were diluted about $1:10^3$ with 95% EtOH. Of the two λ_{max} peaks in isooctane, the lower wavelength peak is always the more intense; the listed ϵ corresponds to this more intense band.

Table II. Effect of Substituents on the ^1H NMR Spectra of Isoindoles and Assessment of Isoindole Aromaticity[a]



	tert-Butyl adduct (R = *t*-Bu)		Ethanedithiol dimer adduct (R = $CH_2\rightarrow_2$)		ET adduct (R = Et)		MERC adduct (R = CH_2CH_2OH)		Di-*tert*-butyl adduct (R = *t*-Bu; C_3–H = C_3–S-*t*-Bu)	
Proton	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ
C_3	7.28 (broad singlet)		7.21 ($J \sim 0.75$ Hz)		7.32 ($J \sim 0.75$ Hz)		7.31 ($J \sim 0.75$ Hz)			
C_4, C_7	7.4–7.8		7.3–7.8		7.4–7.7		7.4–7.7		7.63–7.84	
C_5, C_6	6.8–7.1		6.8–7.1		6.8–7.1		6.8–7.1		6.95–7.16	
C_8	4.33 (J = 7.3 Hz)	−1.69	4.13 ($J \simeq$ 7.4 Hz)	−1.49	4.30 (J = 7.3 Hz)	−1.66	4.30 (J = 7.5 Hz)	−1.66	4.66 (J = 7.5 Hz)	−2.02
C_9	1.83 ($J \simeq J' \simeq$ 7.3 Hz)	−0.38	1.69 ($J \simeq J' \simeq$ 7.4 Hz)	−0.24	1.84 ($J \simeq J' \simeq$ 7.3 Hz)	−0.39	1.80 ($J \simeq J' \simeq$ 7.5 Hz)	−0.35	1.67 ($J \simeq J' \simeq$ 7.5 Hz)	−0.22
C_{10}	0.85 (J' = 7.3 Hz)	+0.05	0.78 ($J' \simeq$ 7.2 Hz)	+0.12	0.85 (J' = 7.3 Hz)	+0.05	0.81 (J' = 7.5 Hz)	+0.09	0.83 (J' = 7.5 Hz)	+0.07
C_{11}			2.63	+0.05	2.53 (J'' = 7.3 Hz)	0.00	2.68 (J'' = 7.0 Hz)	+0.01		
C_{12}	1.22	+0.18			1.04 (J'' = 7.3 Hz)	+0.31	3.50 (J'' = 7.0 Hz)	+0.20	1.23	+0.17
C_{12}–OH							2.9–3.7			

[a] NMR spectra of ~2 M solutions of MERC and ET adducts formed from 1 equiv of each reagent (see Experimental Section) in CD_3CN were determined at 100 and 60 MHz, respectively. Recrystallized samples of the *tert*-butyl and ethanedithiol dimer adducts (60 MHz spectra) and the di-*tert*-butyl adduct (100 MHz spectrum) were examined in $CDCl_3$. The change in chemical shift of the alkyl substituent protons is expressed as $\Delta\delta$ = (δ in starting material) − (δ in 1).

comparison of the chemical shifts of the alkyl substituent protons of 1 (Table II) vs. the starting compounds reveals three important features. (1) The magnitude of deshielding of the C_8 methylene protons is indicative of appreciable ring current and aromaticity in the isoindole system. However, this ring current is less than that of benzene, as witnessed by the position of the C_{11} methylene protons vs. the CH_2 protons of *S*-ethylthiophenol at δ 3.00.[23] This result confirms previous theoretical calculations[12] and ^1H NMR studies of the isoindole ring protons.[22] (2) The deshielding effect of the ring current

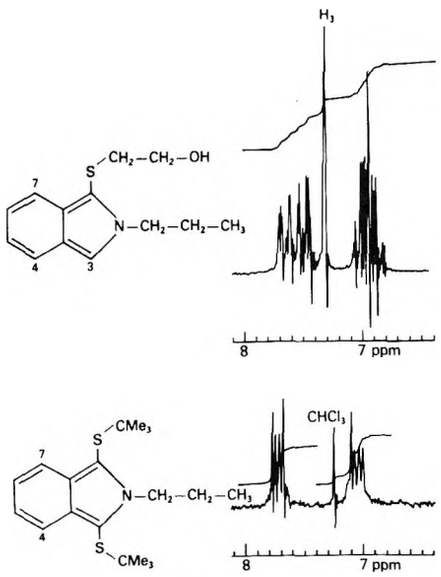
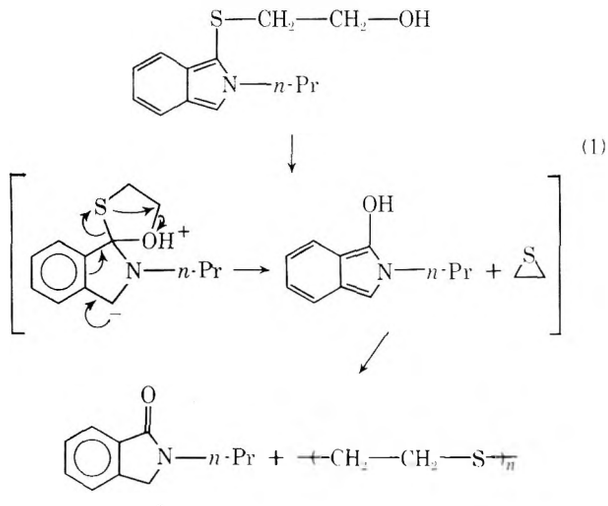


Figure 1. 100-MHz proton NMR spectra of MERC (top) and di-*tert*-butyl (bottom) adducts. Spectra showing the aromatic region for the MERC adduct (the 5 protons of C_3–C_7) in CD_3CN and the di-*tert*-butyl adduct (the 4 protons of C_4–C_7) in $CDCl_3$ are compared.

falls off rapidly with increasing distance from the ring. (3) Those protons δ to the ring system (i.e., C_{10} and C_{12} protons) are shielded. This shielding effect is most noticeable for the thiol substituents and is largest with the ET adduct. In contrast, the chemical shift of the CH_3 group of *S*-ethylthiophenol[23] is unchanged from that of ethanethiol at δ 1.35.

Derivatives of MERC and ET Adducts. The MERC adduct at 0.3 M in 95% EtOH slowly decays at room temperature to give, inter alia, the 2,3-dihydro-1*H*-isoindol-1-one **3** and an insoluble solid which was identified as polyethylene sulfide.[2] This reaction was not appreciably accelerated by the presence of additional water. Under the same conditions, the ET adduct yields a different decomposition product (see below) and no **3**. These results suggest that an intramolecular *nucleophilic attack*, as shown in eq 1, leads to the observed products. A



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major peak at *m/e* 175 (42% of the base peak) in the exact mass spectrum of the MERC adduct that was uniquely identified as $C_{11}H_{13}NO$ (obsd = calcd = 175.0996) further supports this hypothesis. This species, which is the base peak or a major peak in CI mass spectra, could arise from intermolecular attack by the water generated as a reaction byproduct. However, the CI mass spectra of the ET adduct exhibit no such peak even though there is just as much water present.

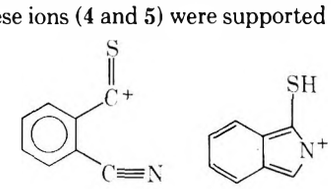
Weakly coppered zinc in acetic acid is efficient in reducing isoindoles to isoindolines.[14,24] When this procedure was applied to the ET adduct, a rapid reaction ensued with the evolution of ethanethiol to give *n*-propylisoindoline. This product presumably was formed by reduction, elimination of ethanethiol with the formation of a cyclic iminium salt, and further reduction.

The MERC and ET adducts react with dienophiles, and a solid 1:1 substitution product of ET adduct and dimethyl acetylenedicarboxylate (DMAC) has been previously reported.[2] These reactions and a detailed examination of the ET adduct–DMAC product are discussed elsewhere.[25]

Other Isoindoles Formed in the Reaction of OPTA and Thiols with Amines. So far, this reaction has proved to be completely general. As anticipated from the results of the *tert*-butyl, ethanedithiol dimer, MERC, and ET adducts, a 1:1:1 ratio of OPTA/thiol/amine gave excellent yields of adducts, as determined by TLC. Development of the TLC plates with I_2 characteristically produced an array of intense, specifically colored spots. Most likely these colors are due to the formation of isoindole–I_2 charge transfer complexes, which is consistent with the π excessive nature of these heterocycles. With dithiol reagents, the above proportions were varied in order to select for the monomer or dimer (e.g., **2**) adduct. All of the adducts were somewhat unstable in solution at room temperature.

Most of the adducts prepared here were not isolated. However, a comparison of the UV spectral properties of the fully characterized *tert*-butyl and ethanedithiol dimer adducts with those of the other adducts in solution established the presence of the isoindole chromophore in each case (Table I). These spectra are quite similar to, but contain much less fine structure than, those of isoindole[20] and *N*-methylisoindole.[26] Of the 1-thio-substituted 2-alkylisoindoles, only the *S*-phenyl and α-carboxyl *N*-alkyl groups cause any noticeable shifts in the λ_{max} wavelengths. The extinction coefficients of the dimeric isoindoles formed with ethanedithiol and dithiothreitol are quite large, but, per isoindole ring, all of the isoindoles examined have much the same ϵ values.

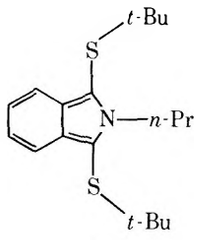
The isoindole structure of each adduct (except for the OPTA/MERC/leucine adduct, which was not examined) was confirmed by the mass spectral molecular weight and fragmentation patterns. In every case, the EI and/or CI[27] mass spectra contained a major peak at *m/e* 146 and/or *m/e* 148. The assigned structures of these ions (**4** and **5**) were supported



	4	5
calcd exact mass:	146.0064	148.0221
obsd exact mass in MERC adduct spectrum:	146.0063	148.0226

by an exact mass determination and appear to be characteristic of isoindoles **1**.

1,3-Dithio-Substituted 2-Alkylisoindoles. Upon standing in solution at room temperature or during attempted recrystallizations, the *tert*-butyl adduct decomposed to give the considerably more stable di-*tert*-butyl adduct **6**. Other isomeric structures were eliminated on the basis of the ^1H NMR spectrum (Figure 1). The absence of a signal attributable to H_3 (or H_1) and the relatively simple and symmetrical two groups of aromatic signals would seem to be diagnostic of the substitution indicated in **6**. As seen for the 1,2-disubstituted isoindoles **1**, the 1,2,3-trisubstituted isoindole **6** also possesses a relatively weak aromatic ring current and causes shielding of the C_{10} and C_{12} protons (Table II). A red shift in the UV



6

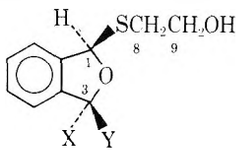
maxima and an increase in the λ_{max} ϵ for the di-*tert*-butyl adduct, compared to the *tert*-butyl adduct (Table I), appear to be characteristic of this substitution pattern. Similar changes have previously been observed for 1,3-diphenyl- vs. 1-phenylisoindoles.[28]

The formation of **6** does not occur by reaction of *tert*-butylthiol with the *tert*-butyl adduct since an excess of *tert*-butylthiol during the production of *tert*-butyl adduct[10] yields virtually no di-*tert*-butyl adduct. Di-*tert*-butyl sulfide, possibly formed during the decomposition of *tert*-butyl adduct, could undergo electrophilic attack on the remaining *tert*-butyl adduct to give **6**. However, when 1.5 equiv of di-*tert*-butyl sulfide was added to almost pure *tert*-butyl adduct, no increased rate of production of **6** was observed. Thus, the di-*tert*-butyl adduct may arise from a disproportionation, or autoxidation,[29] reaction of the *tert*-butyl adduct.

MERC and thiophenol adducts, and especially the ET adduct,[18] are observed to slowly give unisolated decomposition products that behave similarly to the di-*tert*-butyl adduct. Whether they are the analogous 1,3-dithio-substituted isoindoles remains to be established.

Formation of 1,3-Disubstituted 1,3-Dihydroisobenzofurans as Intermediates in the OPTA Reaction. The first operational step in the reaction of OPTA and thiols with primary amines is to combine OPTA and thiol. Since all of the thiols we have examined gave an excellent yield of the isoindole **1**, we expected that each thiol would follow the same basic course of reaction with OPTA. In fact, the results were highly variable. When each thiol was combined with 1 equiv of OPTA, some adduct was always observed by TLC with those thiols carrying functional groups capable of hydrogen bonding while the alkyl- and arylthiols gave no apparent reaction. All attempts to isolate the OPTA/MERC reaction product failed.

A 1:1 OPTA/MERC adduct was suggested by CI mass spectra. Further analysis of the reaction in situ led to the assignment of the diastereomeric 1,3-dihydroisobenzofurans **7** to the unstable OPTA/MERC adducts. The presence of two



7a, X = H; Y = OH
b, X = OH; Y = H

hydroxyl groups in the OPTA/MERC adduct was deduced from the observation of two single proton ^{1}H NMR signals with temperature dependent chemical shifts ($\Delta\delta$ = 0.99 and 0.80 Hz/°C). The existence of an unequal mixture of the diastereomers **7a** and **7b** was most readily seen by the two sets of ^{1}H NMR signals of unequal intensity assigned to the C_3–OH and C_8 methylene protons and the C_9 methylene signals at 56 °C. The major component of this diastereomeric mixture is postulated to be **7a**, which is capable of being stabilized via intramolecular hydrogen bonding, on the basis of a lower OH group frequency in the IR spectrum of the MERC adduct (~3340 cm^{-1}) as compared to the ET adduct (~3400 cm^{-1}). The ^{1}H NMR spectrum of the OPTA/ET adduct exhibits signals which can be assigned to a structure analogous to **7**. However, analysis of the spectrum revealed that only ~20% of the OPTA/ET mixture was present as the 1,3-dihydroisobenzofurans vs. ~85% in the OPTA/MERC solution. A reversible increase in the residual OPTA aldehyde signal at δ 10.1 with increasing temperature indicates that the MERC adducts are in equilibrium with the starting materials.

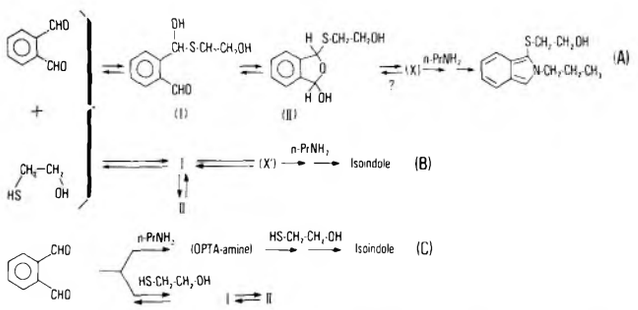


Figure 2. Possible mechanistic pathways for the reaction of OPTA and MERC (or thiol) with *n*-propylamines (or primary amines) to give 1-alkyl(and aryl)thio-2-alkylisoindoles.

Mechanism of the Reaction of OPTA and Thiol with Primary Amines. Two general observations indicate that a 1,3-dihydroisobenzofuran does not react directly with added primary amine. First, while **7** could easily give rise to reactive structures, the intact **7** should be totally unreactive toward added primary amine. Second, the amount of dihydroisobenzofuran formed is very sensitive to the structure of the thiol added to OPTA, and yet all OPTA/thiol solutions react extremely rapidly, even at 0 °C, to give the appropriate isoindole.

Of the three basic schemes (Figure 2) considered for the complete OPTA reaction mechanism, initial reaction of the amine with OPTA, where the formation of II is a nonproductive side reaction (pathway C), was eliminated for two reasons. First, when OPTA and *n*-PrNH$_2$ were mixed under the same conditions used to form isoindoles **1**, a rapid reaction ensued where the color of the solution turned yellow and finally a greenish black within 4 min at 0 °C. In contrast, addition of *n*-PrNH$_2$ to OPTA/thiol solutions gave colorless or light yellow solutions after 10 min at room temperature. These colored products may be related to the unstable colored pigments formed in the reaction of o-acetylbenzophenone with primary amines.[30] Second, the amount of isoindole formed is severely reduced by adding the amine to OPTA before adding the thiol. Such addition sequences are also reported to decrease the yield of fluorescent product.[3] Addition of OPTA to a MERC/*n*-propylamine solution at 0 °C or room temperature gave essentially normal yields of the MERC adduct.

Conceivably a reactive intermediate X, or X′, might not form spontaneously in OPTA/thiol solutions but rather could be generated by the presence of added amine. However, the addition of up to 2 equiv of triethylamine caused no perceptible change in the TLC behavior of the OPTA/MERC solution. On the basis of these results, the predicted unreactivity of **7** and the insensitivity of yields of isoindoles **1** to variations in the relative amounts of dihydroisobenzofurans vs. OPTA + thiol, we presently favor pathway B and the scheme in Figure 3. The ability of thiol, when added with amine to OPTA, to eliminate virtually all of the color formed in the reaction of amine with OPTA is consistent with a more rapid addition of thiol than amine to OPTA. Intramolecular hydrogen bonding in the OPTA/thiol addition product, as has been observed with the closely related *o*-(dimethylaminomethyl)benzyl alcohol,[31] would make the affected carbonyl more susceptible to attack by amine than the carbonyls of OPTA. Protonation of OH vs. SR in the imine intermediate

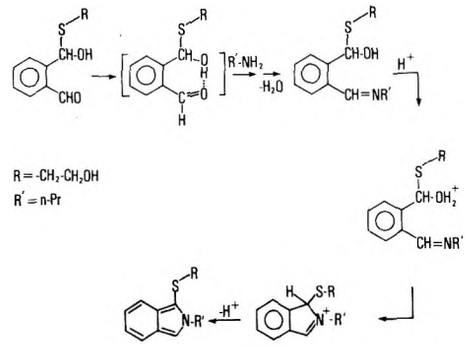


Figure 3. Proposed mechanism for OPTA reaction to give isoindoles.

would be kinetically controlled by the greater basicity of OH to give, after a partially S_N1-like intramolecular reaction, the protonated isoindole and finally **1**. This mechanistic scheme will also account for the lack of fluorogenic reaction with secondary amines[3,6] and primary amines in low pH solutions.[3,4]

Conclusions

We have described a new method of entry into the isoindole ring system and, in particular, the preparation of previously unknown 1-alkyl(and aryl)thio-2-alkylisoindoles. Most of these isoindoles **1** were not isolated but were identified in solution on the strength of spectral data and comparisons with two fully characterized, isolated adducts. The formation of **1** proceeds rapidly under mild, stoichiometric conditions and in very high yield, so there is little need for purification before studying the physical properties or performing further chemistry. This approach is directly supported by the isolation of analytically pure ethanedithiol dimer adduct **2** in 93% yield from the initial reaction solution. The procedure reported here is exceedingly simple and appears to be quite general. In fact, we were surprised that lowering the nucleophilic character of the thiol (i.e., thiophenol) or increasing the steric bulk α to the thiol (i.e., *tert*-butylthiol) had no obvious effect on the rate or yield of the overall reaction.

The isoindoles **1** are much more stable than isoindole itself.[20] Aryl,[24,28] halo,[13,15] and N substitution[32] are usually required for enhanced stability. Very few nonhalogen hetero-substituted isoindoles have reached our attention.[13,16,17] The 1-thio-substituted isoindoles prepared here appear more stable than the isologous 1-alkoxy derivatives.[16] The factors responsible for this stabilization are not understood but may be partially due to d-orbital overlap.

In spite of the aromatic character of isoindoles, they are hyperreactive at positions 1 and 3,[12] as seen by their reaction with dienophiles,[12,16] such as dimethyl acetylenedicarboxylate,[25] and acylating agents.[12,17] This apparent dichotomy has been ascribed to the relatively low energy difference between isoindole and the transient benzene derivative which is formed during electrophilic attack.[33] These same considerations may also explain how this π excessive aromatic heterocycle can undergo an apparent intramolecular nucleophilic reaction (i.e., eq 1). Further support for an intramolecular attack of the OH group of the MERC adduct derives from the observations that the MERC adduct decays faster than the ET adduct in aqueous buffers and that complexation of the OH group inhibits the decay of the MERC adduct.[18,19]

Experimental Section

Materials. OPTA (Aldrich) was recrystallized with a hot filtration from petroleum ether and stored at room temperature in the dark. MERC, ET, methyl mercaptoacetate (all from Eastman), *tert*-butylthiol, thiophenol, ethanedithiol, L-leucine, *n*-propylamine (all from Aldrich), and dithiothreitol (Calbiochem) were used as received. Isooctane (Aldrich gold label) and 95% ethanol (Pharmco) were found to be suitable for use without further purification. Hydro Services deionized water, which was subsequently distilled, was used to prepare 0.5 M $Na_2B_4O_7 \cdot 10H_2O$ (Allied Chemical). Silica gel (GF) and neutral alumina (GF) TLC plates were purchased from Analtech.

Instrumentation. Melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Perkin-Elmer 237B grating infrared and Carey 14 spectrophotometers were used to record IR and UV spectra, respectively. NMR spectra were acquired at 60 (Varian A-60) or 100 MHz (Varian HA-100 spectrometer). Low-resolution mass spectra were obtained on Hitachi Perkin-Elmer RMU-6E (electron impact [EI] mode) or Finnigan 1015D (chemical ionization [CI] mode) spectrometers. A Jeol JMS-015G-2 spectrometer with an Ionomet photoplate was used for the high-resolution mass spectra. Analyses were performed by the Microanalytical Section of the Laboratory of Chemistry, NIAMDD, Bethesda, Md.

***tert*-Butyl Adduct.** Method A utilized 1 equiv of each reagent. A solution of OPTA (163 mg, 1.216 mmol) and *tert*-butylthiol (0.137 mL) in 1.2 mL of 95% EtOH was placed in ice for 10–15 min following 10 min at room temperature. The addition of *n*-propylamine (0.1 mL) gave an exothermic reaction, producing a yellow-orange solution. Brief (~5 s) cooling of the mixture in ice initiated crystallization which proceeded efficiently at room temperature. After cooling at 0 °C, an 86% yield (259 mg) of pale yellow, mica-like plates (mp 48.0–56.5 °C) was obtained. Three rapid recrystallizations from petroleum ether gave analytically pure *tert*-butyl adduct as almost colorless blocks: mp 58.3–59.0 °C; IR (Nujol) ~2900, 1460, 1364, 1317, 1162, 767, and 747 cm^{-1}. Conventional EI mass spectrometry gave peaks (% abundance in parentheses) at *m/e* 247 (M^+, 5.5), 191 (M − isobutylene, 63), 148 (191 − C_3H_7, 86), and 57 (Me_3C, 100). See Tables I and II for UV and ^1H NMR data. Anal. Calcd for $C_{15}H_{21}NS$: C, 72.82; H, 8.56; N, 5.66; S, 12.96. Found: C, 73.15; H, 8.46; N, 5.42; S, 12.56.

Method B involves the use of excess thiol. To 163 mg of OPTA (1.216 mmol) in 0.568 mL of 95% EtOH was added 0.548 mL of *tert*-butylthiol (4.861 mmol). After 15 min at room temperature and then again at 0 °C, *n*-propylamine (0.1 mL, 1.216 mmol) was added to produce an exothermic reaction and a bright yellow solution containing >90% of the *tert*-butyl adduct (by TLC; after I_2 visualization, the adduct was green-brown on silica gel and black on neutral alumina). After removing the volatile components under a stream of nitrogen, the residue was dissolved in a minimum amount of petroleum ether at room temperature to give a two-phase solution which, when cooled to 0 °C, yielded 199 mg (66%) of the *tert*-butyl adduct as clear, light yellow blocks (mp 58.5–59.5 °C).

Ethanedithiol Dimer Adduct 2. Reaction of 163 mg of OPTA (1.216 mmol), 51 μL of ethanedithiol (0.608 mmol), and 100 μL of *n*-propylamine in 2.28 mL of absolute EtOH was accomplished as for the preparation of the *tert*-butyl adduct (method A) to give a clear colorless solution which was allowed to warm to room temperature in the dark. Less than 1 min after adding the amine, the reaction mixture suddenly became a white emulsion from which solid soon began to crystallize. After 10 min at room temperature and 30 min at 0 °C, the crystalline product was isolated by centrifugation, washing with 10 mL of 95% EtOH at 0 °C, and recentrifugation to give, after drying under vacuum, 231 mg (93% yield) of small analytically pure, off-white needles (mp 124.5–130.5 °C). The adduct was purple-black on neutral alumina after I_2 visualization. Mass spectral[27] peaks were observed at *m/e* 408 (M^+, 2), 190 (100), and 148 (80); IR (Nujol) 3125, 3060, 1458, 1321, 1176, 769, and 752 cm^{-1}. See Tables I and II for UV and ^1H NMR data. Anal. Calcd. for $C_{24}H_{28}N_2S_2$: C, 70.54; H, 6.91; N, 6.86. Found: C, 70.12; H, 7.05; N, 6.60.

General Procedure for Preparation of Isoindoles 1. A 1 M solution of each reagent was prepared in 95% EtOH and stored at 0 °C. Some decomposition of 1 M OPTA was observed at 0 °C, but solutions could be stored for up to 6 months at −20 °C with almost no decomposition. While very concentrated solutions of the adducts were used to obtain the IR or NMR spectra (e.g., OPTA in enough benzene to affect dissolution followed by thiol, cooling, *n*-propylamine, and absorption of the generated water with 3A molecular sieves gave the IR sample), the usual reactions employed the above 1 M solutions. Thus, 100 μL each of 1 M OPTA and 1 M thiol were mixed at room temperature, and the mixture was allowed to stand for 10 min, cooled at 0 °C for 10 min, and then treated with 100 μL of 1 M *n*-propylamine. After 1 min at 0 °C followed by 10 min at room temperature, these ~0.33 M solutions of the various isoindoles were stored at 0 °C.

Exceptions to this general procedure include the preparations using leucine, where 50 μL of a 1:1 mixture of 1 M OPTA/1 M MERC at 0 °C was added to 0.25 mL of 0.1 M leucine in 0.05 M sodium tetrabo-

rate, and thiols such dithiothreitol and ethanedithiol which contain two SH groups. An eightfold excess of these thiols was used when the monomer adduct was desired; 0.5 equiv of the thiol yielded the bridged diisoindole or dimer adduct. When the ethanedithiol dimer was prepared by this method, a 95% EtOH insoluble white solid crystallized out of the reaction solution. This solid was dissolved immediately in EtOAc (final concentration, 2.0×10^{-2} M) and used for all subsequent UV and fluorescence[18] measurements. See Table I for the characteristic UV spectral properties of these isoindoles.

β-Mercaptoethanol Adduct. An exact mass determination and a full ^{1}H NMR spectrum of this adduct have been previously reported.[2] This adduct gave a red to red-brown color with I_2 staining on neutral alumina and silica gel, respectively: IR (~10 M in benzene) 3350, 3030, 1460, 1320, 1170, 759, and 747 cm^{-1}; EI mass spectral peaks at *m/e* 235 (M^+, 47), 190 ($M - C_2H_4OH$, 85), 175 ($M - C_2H_4S$, 42), 148 (**5**, 35), and 146 (**4**, 100). See Table II for ^{1}H NMR data.

Ethanethiol Adduct. On silica gel, or neutral alumina, this adduct turns brown, or blue-black, with I_2 staining: IR (~10 M in benzene) 3030, 1460, 1320, 1170, 758, and 746 cm^{-1}; CI[27] mass spectral peaks at *m/e* 219 (M^+, 44), 190 ($M - C_2H_5$, 100), and 148 (**5**, 81). See Table II for ^{1}H NMR data.

2,3-Dihydro-1*H*-isoindol-1-one 3. An approximately 1 M solution of the MERC adduct, prepared from 1 equiv (0.89 mmol) each of OPTA, MERC, and *n*-propylamine in 0.7 mL of acetonitrile and containing 7 equiv of water, was allowed to decompose for two weeks in the dark at room temperature. The insoluble solid that formed was removed by filtration (see below for characterization), and preparative TLC (3:1 benzene/ethyl acetate on neutral alumina) of the concentrated filtrate gave a 78% yield (123 mg) of the cyclic amide as an almost TLC pure yellow liquid. After two weeks at −20 °C, a low melting (~30 °C) solid was formed. Four recrystallizations from ~1:1 petroleum ether/ether (dissolved at room temperature and cooled to −50 °C in a $CHCl_3/N_2$ slush bath) gave colorless needles whose melting point (33.1–34.7 °C) was similar to that of the known *N*-ethyl derivative (44–45 °C).[34] The exact mass determination and IR and 60-MHz NMR spectra have been reported elsewhere.[2] The low-resolution mass spectrum (EI mode) gave peaks at *m/e* 175 (M^+, 28), 160 ($M - Me$, 2), 146 ($M - C_2H_5$, 100), and 91 (36).

The above insoluble solid of the decomposed MERC adduct solution was washed with acetone to give 2.2 mg of a pale green solid. Similar preparations of polymer (mp 111.7–115.0 °C) gave CI (isobutane) mass spectral peaks at *m/e* $105 + n \times 60$, $123 + n \times 60$, $137 + n \times 60$, $139 + n \times 60$, and $153 + n \times 60$, where $n = 0$–4, were usually observed. "Authentic" polyethylene sulfide, formed from the boron trifluoride catalyzed reaction of ethylene sulfide in MeOH, decomposed at 180–187 °C and gave an IR spectrum almost identical with that of the above lower melting polymer. Sulfur analysis: calcd for $+CH_2CH_2-S+_n$, 53.34%; obsd for MERC adduct reaction product, 52.41%; obsd for "authentic" polymer, 51.74%.

***n*-Propylisoindoline.** ET adduct (0.25 mmol; formed in 0.1 mL of acetonitrile from 1 equiv of each reagent) was added to 2 mL of glacial acetic acid to give a bright green solution. Immediately, 0.17 g of fresh, weakly coppered zinc dust (~2.5 mmol) was added at room temperature during 5 min. After 20 min, 6 mL of H_2O was added to the red-brown solution, which smelled heavily of ethanethiol. After 2 h, filtration and washing with CH_2Cl_2 of the now yellow solution followed by addition of concentrated NH_4OH to pH >9, extraction (40 mL CH_2Cl_2), and removal of the dried ($MgSO_4$) solvent under reduced pressure gave a 68% yield (28.5 mg) of the crude amine as a light brown liquid. The IR spectrum (Nujol) was characteristic of 1,3-unsubstituted N-substituted isoindolines, i.e., no aromatic bands from 1600–1500 cm^{-1} and a band at ~2765 cm^{-1},[35] which was found at 2786 cm^{-1} here. Mass spectral peaks were observed at *m/e* 162 (MH^+, 100) in the CI mode with isobutane and at *m/e* 161 (M^+, 14), 160 ($M - H$, 13), 132 ($M - C_2H_5$, 100), 118 ($M - C_3H_7$, 24), and 105 ($M - C_3H_6N$, 34) in the EI mode.

Di-*tert*-butyl Adduct 6. *tert*-Butyl adduct (mp ~48–54 °C) gave, upon recrystallization from methanol or acetonitrile, a low yield of slightly impure di-*tert*-butyl adduct (mp 124–126 °C). Alternatively, the *tert*-butyl adduct in acetonitrile (± heat; ± added *tert*-butylthiol) for 1–2 weeks gave 15–40% yields of material after preparative TLC (3:1 petroleum ether/benzene on silica gel). A second preparative TLC treatment and two recrystallizations from acetonitrile gave analytically pure di-*tert*-butyl adduct **6**: mp 126.2–127.0 °C; IR (Nujol) ~2880, 1453, 1363, 1314, 1163, and 751 cm^{-1}. Mass spectral peaks were observed at *m/e* 336 (MH^+, 100) in the CI mode with isobutane and at *m/e* 335 (M^+, 5), 279 ($M -$ isobutylene, 3), 223 ($M -$ 2 isobutylene, 32), 146 (96), and 57 (Me_3C^+, 100) with the EI mode. See Tables I and II for UV and ^{1}H NMR data. Anal. Calcd. for $C_{19}H_{29}NS_2$: C, 68.00; H, 8.71; N, 4.17; S, 19.11. Found: C, 68.21; H, 8.76; N, 4.31; S, 18.88.

1,3-Dihydroisobenzofurans (e.g., 7). The same procedure that was used to form the isoindoles **1** was followed except that no amine was added. With MERC, CI[27] mass spectral peaks were observed at *m/e* 212 (M^+, 0.1), 194 ($M - H_2O$, 0.1), 167 ($M - C_3H_4OH$, 0.2), 135 ($M - SC_2H_4OH$, 72), 134 (38), and 77 (100). The 60-MHz ^{1}H NMR spectrum ($CDCl_3$ at 23.5 °C) of OPTA/MERC exhibited the following: aromatic H at δ 7.33 (4 H); 1-H and 3-H centered at δ 6.45 (2 H) as two pairs of unequal singlets; 3-OH as two broad, unequal signals at δ 5.85 and 5.98 (1 H); 9-OH at δ ~3.95 (broad) and 9-H at δ 3.67 (triplet, J = 5.5 Hz) (total of 3 H); and 8-H as two unequal triplets (J = 5.5 Hz) at δ 2.69 and 2.65 (2 H). A linear variation in the chemical shift of C_3–OH (0.99 Hz/°C) and C_9–OH (0.80 Hz/°C) signals was observed from −43 to +56 °C.

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Registry No.—**3**, 61214-23-1; **7a**, 66161-47-5; **7b**, 66161-37-3; HS–R (R = Et), 75-08-1; HS–R (R = CH_2CH_2OH), 60-24-2; HS–R (R = *t*-Bu), 75-66-1; HS–R (R = Ph), 108-98-5; HS–R (R = CH_2CH_2SH), 540-63-6; HS–R (R = *threo*-$CH_2CHOHCHOHCH_2SH$), 3483-12-3; HS–R (R = CH_2COOMe), 2365-48-2; L-leucine, 61-90-5; propylamine, 107-10-8; *o*-phthalaldehyde, 643-79-8; polyethylene sulfide, 24936-67-2; *N*-propylisoindoline, 66161-38-4.

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Synthesis of New Nitrogen-Bridged Heterocycles. Reaction of Pyridinium *N*-Imines with Cyclopropenones

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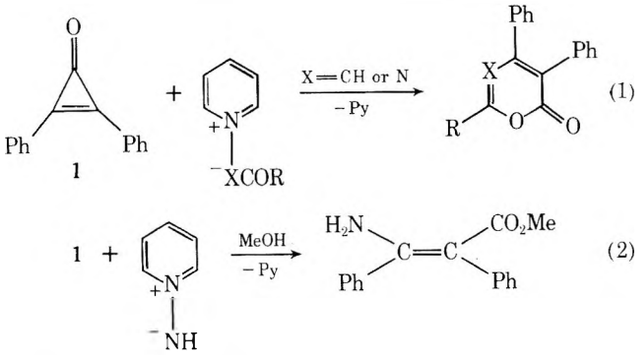
Pyridinium *N*-imine salts **3** and **5–8** reacted smoothly with methylphenylcyclopropenone (**2**) in methylene chloride in the presence of triethylamine at room temperature to give the corresponding 2-methyl-4-phenyl-3*H*-pyrido[1,2-*b*]pyridazin-3-ones **14–19** in fairly good yields. 4,4a-Dihydro intermediates **10–13** were isolated from the reactions of **3, 4,** and **9.** Reaction of **2** with **3** in methanol containing triethylamine afforded β-amino ester **22** in addition to **14.** Dipropylcyclopropenone (**24**) did not react with pyridinium *N*-imine salts in methanol containing triethylamine at room temperature, but did furnish 2,4-dipropyl-3*H*-pyrido[1,2-*b*]pyridazin-3-ones **25–28** with **3** and **5–7** under reflux conditions. Possible mechanisms of this reaction are discussed.

The cycloaddition reactions of pyridinium *N*-imines and pyridinium methylides with activated acetylenes serve as useful synthetic routes to a variety of pyrazolopyridines[1] and indolizines,[2] respectively. Although extension of these reactions to cyclopropenones would appear to offer promise for the preparation of other interesting bicyclic systems, in actual fact pyridinium ylides tend to react as nucleophiles with diphenylcyclopropenone (**1**) with loss of pyridine occurring in the process (eq 1[3,4] and 2[5]). Our observation[6] of the formation



of a 3*H*-pyrido[1,2-*b*]pyridazin-3-one as the result of a possible 1,3-dipolar cycloaddition reaction between pyridinium *N*-imine and methylphenylcyclopropenone represents the first evidence of behavior analogous to that of activated acetylenes for a cyclopropenone in these reactions. More recently, the reaction of pyridinium dicyanomethylide with **1** has been reported to yield a product of 1,3-dipolar cycloaddition.[7] However, utilization of 4-methylpyridinium dicyanomethylide in this reaction afforded a complex mixture of products, suggesting that the behavior of the parent ylide may be an exception. This paper describes the preparation of 3*H*-pyrido[1,2-*b*]pyridazin-3-ones from the reactions of various pyridinium *N*-imines with methylphenylcyclopropenone and di-*n*-propylcyclopropenone and the isolation of 4,4a-dihydro intermediates in certain cases.

Results and Discussion

The reactions of methylphenylcyclopropenone (**2**) with pyridinium *N*-imine salts **3–9** were carried out in methylene chloride in the presence of triethylamine (for **3–8**) or potassium carbonate (for **9**)[8] at room temperature. The results are summarized in Scheme I.

Reaction of the parent **3** with **2** afforded, after 17 h, both **10** (69%) and **14** (27%), while a 65-h reaction gave **10** (20%) and **14** (70%). A ready transformation of **10** to **14** was observed upon recrystallization attempts or excessive exposure to column chromatography. Also, **14** was obtained quantitatively from a benzene solution of **10** that had been heated under reflux for 16 h. The elemental analysis, NMR integration, and mass spectrum of **14** indicated that it was a dehydrogenation product of a 1:1 adduct. Evidence for the isomer bearing phenyl in the 4 position was obtained from the NMR spectrum of the 1:1 adduct **10,** which showed a one hydrogen doublet (J = 18 Hz) at δ 3.75 assigned to H_4. The magnitude of the coupling constant suggested a *trans*-diaxial relationship for H_4 and H_{4a}. Reaction of **4** with **2** produced **11** (19%, 35-day reaction time), whose NMR spectrum showed a one hydrogen singlet at δ 3.40, thus confirming the assignment. The 17-h reactions of other methyl-substituted pyridinium *N*-imine salts **5–8** gave the corresponding **15–19** in 62, 40, 20, 71, and 22% yields, respectively, where **16** and **17** are the two expected regioisomers from **6.** No dihydro intermediates were isolated in these cases. The observed predominance of cycloaddition at the sterically *less* hindered site (2:1) in the reaction of the unsymmetrically substituted **6** is, to the best of our knowledge, without precedence for this reagent. The cycloadditions of ethyl propiolate with a variety of 3-substituted pyridinium *N*-imines have been found to occur preferentially at the *more* hindered position, regardless of the electron-donating or electron-withdrawing character of the substituent.[1] Recently, the reaction of **6** with 2-phenylazirine has been reported to involve mainly cycloaddition at the *more* hindered site, where that of a pyridinium *N*-imine bearing at electron-withdrawing group at the 3 position, i.e., **9,** gave exclusively inverse orientation to the *less* hindered position.[9] With the objective of determining the effect of such a change in the electronic nature of the 3 substituent in **3** upon orientation in cycloaddition with **2,** the reaction of **9** was examined. A 12-day reaction (using potassium carbonate as base) produced only **12** (38%) and **13** (42%), whose NMR spectra showed characteristic one hydrogen doublets at δ 3.90 and 4.05 (J = 17 Hz), respectively. Treatment of these 4,4a-dihydro intermediates with palladium on carbon (10%) resulted in quantitative dehydrogenation to the corresponding aromatized derivatives **20** and **21,** whose H_8 multiplicities (see Table I) permitted the assignments of structures **12** and **13.** Thus, although a slight preference for the *more* hindered site was observed for the reaction of **9** with **2,** the change in the electronic character of the 3 substituent here did not affect orientation as dramatically as in the case of 2-phenylazirine above.

When the reaction of **2** with **3** was carried out in methanol containing triethylamine (24 h) the β-amino ester **22** was isolated as a pentane soluble oil (31%) in addition to **14** (67%).

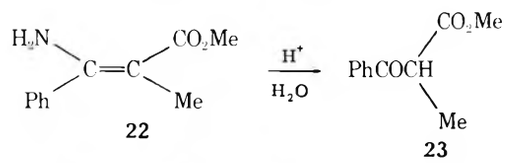


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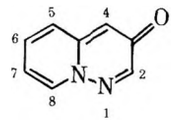
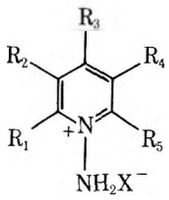
Table I. ^{1}H-NMR Spectral Data of Pyridopyridazinones ($CDCl_3$)

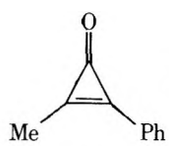


Compd	C_2	C_4	C_5	C_6	C_7	C_8
14	2.48 (s)	7.42 (s)	7.20 (m)		6.64 (m)	8.18 (d) (J = 7.0 Hz)
15	2.57 (s)	7.34 (s)	7.10 (m)		6.60 (m)	2.69 (s)
16	2.48 (s)	7.34 (s)	7.07 (m)		2.23 (s)	7.90 (s, br)
17	2.48 (s)	7.34 (s)	1.76 (s)	7.00 (d, br) (J = 7.0 Hz)	6.56 (t) (J = 7.0 Hz)	8.03 (d) (J = 7.0 Hz)
18	2.48 (s)	7.40 (s)	6.94 (s, br)	2.23 (s)	6.50 (dd) (J = 7.0, 1.5 Hz)	8.03 (d) (J = 7.0 Hz)
19	2.51 (s)	7.31 (s)	1.73 (s)	6.92 (s)	2.23 (s)	7.95 (s)
20	2.55 (s)	7.40 (m)	7.18 (m)			8.53 (s, br)
21	2.54 (s)	7.40 (m)		7.65 (dd) (J = 7.0, 1.5 Hz)	6.65 (t) (J = 7.0 Hz)	8.35 (dd) (J = 7.0, 1.5 Hz)
25	2.89 (t) 1.60 (m) 1.00 (t) (all J = 7.0 Hz)	2.78 (t)	7.33 (m)		6.66 (m)	8.13 (d) (J = 7.0 Hz)
26	3.00 (t) 1.80 (m) 1.07 (t)	2.88 (t) 1.05 (t)	7.33 (m)		6.67 (m)	2.73 (s)
27	2.89 (t) 1.66 (m) 1.00 (t)	2.76 (t)	7.26 (m)		2.30 (s)	8.00 (s)
28	2.92 (t) 1.68 (m) 1.00 (t)	2.78 (t)	7.12 (s, br)	2.37 (s)	6.55 (dd) (J = 7.0, 1.5 Hz)	8.06 (d) (J = 7.0 Hz)

Scheme I

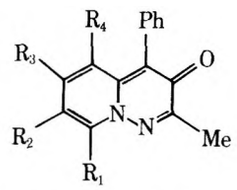


3, $R_1 = R_2 = R_3 = R_4 = R_5 = H$; X = I
4, $R_1 = R_5 = Me$; $R_2 = R_3 = R_4 = H$; X = I
5, $R_1 = Me$; $R_2 = R_3 = R_4 = R_5 = H$; X = I
6, $R_1 = H$; $R_2 = Me$; $R_3 = R_4 = R_5 = H$; X = I
7, $R_1 = R_2 = H$; $R_3 = Me$; $R_4 = R_5 = H$; X = I
8, $R_1 = H$; $R_2 = R_4 = Me$; $R_3 = R_5 = H$; X = I
9, $R_1 = H$; $R_2 = CN$; $R_3 = R_4 = R_5 = H$; X = OMes



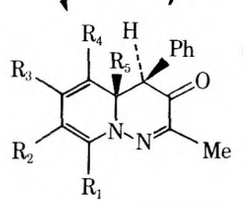
2

CH_2Cl_2, base for **3**, **5–8**



14, $R_1 = R_2 = R_3 = R_4 = H$
15, $R_1 = Me$; $R_2 = R_3 = R_4 = H$
16, $R_1 = H$; $R_2 = Me$; $R_3 = R_4 = H$
17, $R_1 = R_2 = R_3 = H$; $R_4 = Me$
18, $R_1 = R_2 = H$; $R_3 = Me$; $R_4 = H$
19, $R_1 = H$; $R_2 = R_4 = Me$; $R_3 = H$
20, $R_1 = H$; $R_2 = CN$; $R_3 = R_4 = H$
21, $R_1 = R_2 = R_3 = H$; $R_4 = CN$

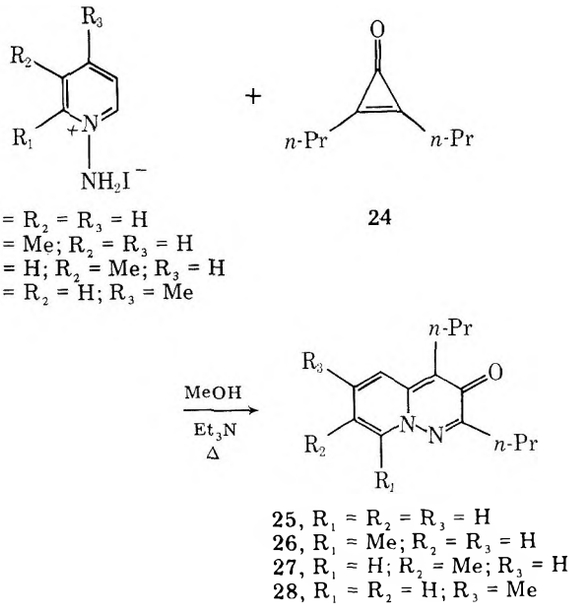
CH_2Cl_2, base for **3**, **4**, **9**



10, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
11, $R_1 = R_5 = Me$; $R_2 = R_3 = R_4 = H$
12, $R_1 = H$; $R_2 = CN$; $R_3 = R_4 = R_5 = H$
13, $R_1 = R_2 = R_3 = H$; $R_4 = CN$; $R_5 = H$

A quantitative hydrolysis of **22** to the β-keto ester **23** occurred on standing or on treatment with 10% sulfuric acid. The formation of **22** is viewed as a consequence of initial conjugate addition of pyridinium N-imine on the cyclopropenone ring with subsequent ring opening at the PhC–CO bond. This mode of ring opening has been observed in the reactions of **2** with 2-aminopyridines.[10] Although pyridinium N-imines have been found to react as 1,3-dipolar[1] or nucleophilic[11] reagents, the reaction of **2** with **3** in methanol apparently represents the first example of a possible dual behavior for this system in a

Scheme II



3, $R_1 = R_2 = R_3 = H$
5, $R_1 = Me; R_2 = R_3 = H$
6, $R_1 = H; R_2 = Me; R_3 = H$
7, $R_1 = R_2 = H; R_3 = Me$

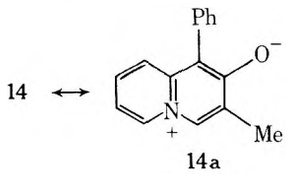
24

25, $R_1 = R_2 = R_3 = H$
26, $R_1 = Me; R_2 = R_3 = H$
27, $R_1 = H; R_2 = Me; R_3 = H$
28, $R_1 = R_2 = H; R_3 = Me$

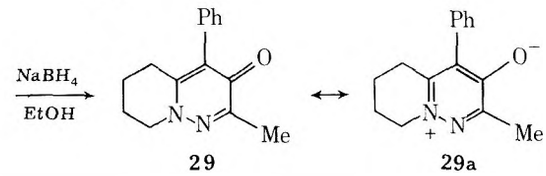
single reaction. The formation of both **22** and **14** here as opposed to the exclusive isolation of a β-amino ester in the case of diphenylcyclopropenone (**1**, eq 2) is consistent with the concept of a diminished reactivity in ring opening with nucleophiles for alkyl-substituted cyclopropenones.[10,12,13] The extension of this reaction to di-*n*-propylcyclopropenone (**24**) was therefore considered to be of interest.

No reaction was observed between pyridinium *N*-imines and **24** in methanol containing triethylamine during 5 days at room temperature, suggesting that both pathways are suppressed upon alkyl substitution in the cyclopropenone. Under reflux conditions, however, **24** did react with **3** and **5–7** to afford the corresponding **25–28** in 68 (2 days), 48 (10 days), 26 (12 days), and 53% (5 days) yields, respectively (see Scheme II). No absorption characteristic of methyl ester was observed in the NMR spectra of the crude residues. The adduct **25** from the parent imine **3** was isolated as the hydrate, as indicated by the elemental analysis. From the unsymmetrical **6**, only product **27**, corresponding to cyclization at the *less* hindered site, was observed, albeit in low yield. The ^1H NMR spectra of these adducts are strikingly similar to one another and also to those of **14–21** (see Table I).

While the IR spectra of all 4,4a-dihydro intermediates **10–13** showed characteristic carbonyl absorption at 1680–1690 cm^{-1}, those of the 3*H*-pyrido[1,2-*b*]pyridazin-3-ones **14–21** and **25–28** showed intense absorption below 1600 cm^{-1} only, suggesting that a charge-separated structure, i.e., **14a**, makes an important contribution to the resonance hybrid. This contribution may be reflected in the sodium borohydride reduction of **14** in ethanol, which afforded **29** in 61% yield. The mass spectrum of **29** indicated the incorporation of four hydrogens, while the NMR spectrum contained two 2 H triplets at δ 2.63 and 4.15. The IR spectrum of **29** showed intense absorption at 1605 and 1580 cm^{-1}, demonstrating the important role of an aromatic charge-separated structure, **29a**, in this case also.



14a



29 29a

In Scheme III, possible pathways to the 3*H*-pyrido[1,2-*b*]pyridazin-3-ones are presented for the reactions of **2** with **3–9**. One route (path a) involves initial 1,3-dipolar cycloaddition ($_\pi4_s + _\pi2_s$) of the pyridinium *N*-imines **30** with **2**, followed by opening of the cyclopropanone ring in **31** with transfer of the amino hydrogen to afford **32**. Although the isolated 4,4a-dihydro intermediates **10**, **12**, and **13** are apparently trans, initial formation of a *cis*-4,4a-dihydro intermediate cannot be ruled out, in as much as isomerization, under the basic conditions utilized, might be expected.[14] For this reason, the stereochemistry in **32** is not specified. An alternative route (path b) to **32** involves initial nucleophilic addition of **30** at the Me–C of **2** with proton transfer, followed by homo-1,5-dipolar cyclization ($_\pi4_s + _\sigma2_s$) of the resulting **33** or by cyclization of a 1,6-dipolar species **34** from **33**. This

Scheme III

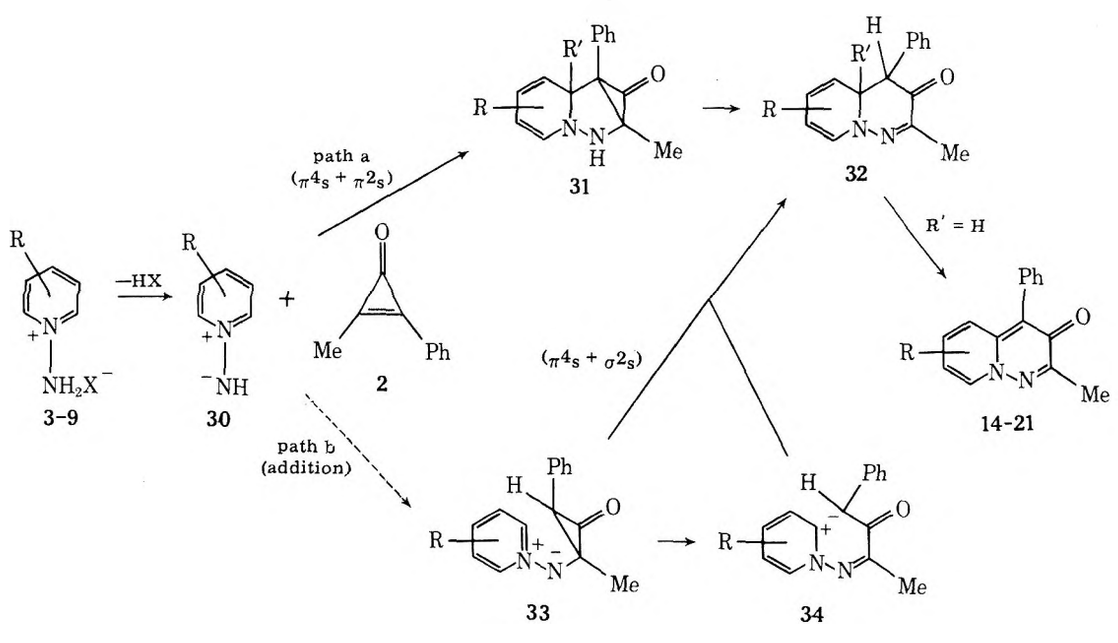


Table II. Results and Some Properties of Pyridopyridazinones

Compd[a]	Registry no.	Reactant: N-Imine	Reactant: Registry no.	Reactant: Cyclopropenone	Yield,[b] %	Mp, °C	IR (KBr), cm^{-1}
14	60047-71-4	**3**	6295-87-0	**2**	96[c]	201–203	1642 (m), 1600, 1580
15	66213-51-2	**5**	7583-90-6	**2**	62	171–173	1631 (m), 1600, 1597
16	66213-52-3	**6**	7583-91-7	**2**	40	142–144	1647 (w), 1601, 1581
17	66213-53-4	**6**		**2**	20	160–162	1640 (w), 1619, 1593
18	66213-54-5	**7**	7583-92-8	**2**	71	142–144	1649 (m), 1600, 1590
19	66213-55-6	8	7585-71-9	**2**[e]	22	165–167	1658 (w), 1612, 1579
20	66213-56-7	(**9**)	59065-90-6	(**2**)	100[d] (38)	205–207	2235, 1645 (w), 1605, 1592
(**12**)	66213-57-8						
21	66213-58-9	(**9**)		(**2**)	100[d] (42)	206–207	2230, 1640 (w), 1610, 1585
(**13**)	66213-59-0						
25	66213-60-3	**3**		**24**[f]	68	41–42	1643 (m), 1574
26	66213-61-4	**5**		**24**	48	80–82	1647 (m), 1592
27	66213-62-5	**6**		**24**	26	96.5–97.5	1660 (w), 1585
28	66213-63-6	**7**		**24**	53	70–71	1652 (m), 1577

[a] Anal. **14:** Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.15; H, 5.26; N, 11.89. **15:** Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.19. Found: C, 76.61; H, 5.64; N, 11.25. **16:** Found: C, 76.52; H, 5.81; N, 11.05. **17:** Found: C, 76.61; H, 5.67; N, 11.27. **18:** Found: C, 76.55; H, 5.76; N, 11.18. **19:** Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.24; H, 6.36; N, 10.46. **20:** Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.47; H, 4.31; N, 16.17. **21:** Found: C, 73.68; H, 4.35; N, 15.99. **25:** Calcd for $C_{14}H_{18}N_2O{\cdot}H_2O$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.45; H, 7.72; N, 11.11. **26:** Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.46; H, 8.29; N, 11.29. **27:** Found: C, 73.65; H, 8.15; N, 11.61. **28:** Found: C, 73.60; H, 8.41; N, 11.50. [b] Reaction times: **14–19,** 17 h; **12, 13,** 12 days; **25,** 2 days (reflux); **26,** 10 days (reflux); **27,** 12 days (reflux); **28,** 5 days (reflux). [c] Combined yields of **10** (69%) and **14** (27%). [d] From **12** or **13.** [e] Registry no. 26307-30-2. [f] Registry no. 698-93-1.

pathway may be contrasted with that suggested for the formation of β-amino ester **22,** wherein nucleophilic addition at the Ph–C of **2** results in rupture of the PhC–CO bond with elimination of pyridine.

The results of the present study, together with those obtained previously[5] with diphenylcyclopropenone, provide an interesting spectrum of reactivity for cyclopropenones in reactions with a reagent capable of both nucleophilic and dipolar behavior, a trend which may find application in the preparation of other novel heterocyclic systems.

Experimental Section

Melting points were obtained on a Mettler PF52 melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Alfred Bernhardt Laboratories, West Germany.

Materials. Pyridinium *N*-imine hydriodides **3–8** and mesitylene sulfonate **9** were prepared by Gösl's[15] and Tamura's[16] methods, respectively. Cyclopropenones **2**[17] and **24**[18] were also synthesized according to the literature.

Reactions of Pyridinium *N*-Imines with Cyclopropenones. A. Reactions with Methylphenylcyclopropenone 2 in Methylene Chloride. An equimolar mixture (2–4 mmol) of pyridinium *N*-imine salt and cyclopropenone **2** was treated with an excess of triethylamine (1.5 mL, 10 mmol) or potassium carbonate (5 g, used only for **9**) in methylene chloride (30–60 mL) at room temperature for 17 h (35 days for **4,** 12 days for **9**) and then the solvent was removed under reduced pressure. The crude residue was extracted with 4 80-mL portions of ether. The combined extracts were concentrated under reduced pressure, and the residue was separated by column chromatography on silica gel.

1. Isolation and Aromatization of Dihydropyridopyridazinones 10–13. Elution with benzene of the above residue from the reactions of **3, 4,** and **9** afforded the cycloadducts which in the cases of **10, 12,** and **13** were aromatized in benzene by heating or treatment with palladium on carbon (10%).

Isolation and Aromatization of 10. From the reaction of **3, 10** was obtained as an orange solid (69%): mp 135–137 °C; IR ($CHCl_3$) 1680, 1655, 1592 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (3 H, singlet), 3.75 (1 H, doublet, J = 18.0 Hz, H_4), 5.05 (3 H, multiplet), 5.95 (1 H, multiplet), 6.80 (1 H, doublet, J = 7.0 Hz, H_8), 7.0–7.5 (5 H, multiplet).

Cycloadduct **10** (0.10 g) was treated in benzene (30 mL) at reflux temperature for 16 h to give **14** quantitatively: mp 201–203 °C (see Table II).

Isolation of 11. From the reaction of **4, 11** was obtained as an orange oil (19%): IR ($CHCl_3$) 1680, 1650, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (3 H, singlet), 2.05 (3 H, singlet), 2.10 (3 H, singlet), 3.40 (1 H, singlet, H_4), 4.97 (2 H, multiplet), 5.60 (1 H, multiplet), 7.30 (5 H, singlet).

Cycloadduct **11** was unstable upon crystallization attempts or excessive exposure to column chromatography, furnishing unidentified decomposition products.

Isolation and Aromatization of 12 and 13. From the reaction of **9, 12** was obtained as an orange solid (38%) from the first fraction to be eluted with benzene: mp 176–177 °C; IR (KBr) 2205, 1690, 1645, 1585 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (3 H, singlet), 3.90 (1 H, doublet, J = 17.0 Hz, H_4), 5.20 (2 H, multiplet), 6.0 (1 H, multiplet), 7.0–7.56 (6 H, multiplet).

From the second fraction to be eluted with benzene there was obtained **13** as a red solid (42%): mp 144–145 °C; IR (KBr) 2200, 1690, 1625, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.16 (3 H, singlet), 4.05 (1 H, doublet, J = 17.0 Hz, H_4), 5.25 (2 H, multiplet), 6.60–7.60 (7 H, multiplet).

Although cycloadduct **12** was stable in benzene solution at reflux temperature and **13** reacted only slowly under these same conditions, a smooth dehydrogenation could be effected using palladium on carbon (10%). Thus, a solution of **12** (0.10 g) in benzene (20 mL) containing palladium on carbon (0.10 g) was heated under reflux for 6 days to afford **20** quantitatively, while a similar treatment of **13** for 1.5 days produced **21** quantitatively (see Table II).

2. Isolation of Pyridopyridazinones 14–19. Elution with benzene–ether (1:1) of the residue from the reactions of **3** and **5–8** afforded the corresponding **14–19** as pale yellow to yellow crystalline solids. These results and some properties of the pyridopyridazinones are summarized in Table II.

B. Reaction of *N*-Imine 3 with Methylphenylcyclopropenone 2 in Methanol. A solution of pyridinium *N*-imine salt **3** (1.110 g, 5 mmol), cyclopropenone **2** (0.576 g, 4 mmol), and triethylamine (1.5 mL, 10 mmol) in 80 mL of dry methanol was allowed to stand for 24 h at room temperature during which time it developed a dark red coloring. The solvent was then removed under reduced pressure and the crude residue was extracted with three 80-mL portions of ether. The combined extracts were concentrated under reduced pressure and this residue was extracted with three 30-mL portions of pentane from which there was obtained 0.240 g (31%) of methyl α-methyl-β-amino-*trans*-cinnamate (**22**) as a pale yellow oil: IR ($CHCl_3$) 3492, 3316, 1660, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (3 H, singlet), 3.69 (3 H, singlet), 6.0–7.0 (2 H, broad), 7.30 (5 H singlet). Hydrolysis of **22** in 10% H_2SO_4 (40 h at room temperature) produced methyl α-benzoylpropionate (**23**) quantitatively, identical in all respects with an authentic sample.[19]

Recrystallization of the pentane-insoluble fraction from methylene

chloride–pentane afforded **14** (0.644 g, 67%), identical to the material isolated from the reaction of **2** with **3** in methylene chloride.

C. Reactions with Dipropylcyclopropenone 24 in Methanol. A solution of pyridinium *N*-imine salt (2.5 mmol), triethylamine (0.75 mL, 5 mmol), and cyclopropenone **24** (0.276 g, 2 mmol) in 50 mL of dry methanol was heated under reflux until the IR spectrum of an aliquot no longer demonstrated the presence of cyclopropenone. The residue of the workup as in A was separated by column chromatography on silica gel using benzene–ether as an eluent. The results are summarized in Table II.

Sodium Borohydride Reduction of 2-Methyl-4-phenyl-3*H*-pyrido[1,2-*b*]pyridazin-3-one (14). Sodium borohydride (80 mg, 2.1 mmol) was added to a solution of **14** (118 mg, 0.5 mmol) in 15 mL of absolute ethanol. After 17 days at room temperature (additional 80-mg portions of sodium borohydride were added on the 6th and 14th days), the solvent was evaporated and the resulting white solid was treated with 10% aqueous ammonium chloride (30 mL). An ether extract (100 mL) was dried over $MgSO_4$, filtered, and evaporated to give a yellow oil which was separated by column chromatography on silica gel using benzene–ether as an eluent to afford 73 mg (61%) of a white solid: mp 164–166 °C; mass spectrum *m/e* (rel intensity) 240 (65, M^+), 239 [100, $(M-1)^+$], 212 [13, $(M-CO)^+$]; IR (KBr) 1605, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.10–2.20 (4 H, multiplet), 2.36 (3 H, singlet), 2.63 (2 H, triplet, J = 6.0 Hz), 4.15 (2 H, triplet, J = 6.0 Hz), 7.05–7.45 (5 H, multiplet). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.97; H, 6.78; N, 11.83.

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Registry No.—**4**, 36012-28-9; **10**, 66213-64-7; **11**, 66213-65-8; **22**, 66213-66-9; **29**, 60047-73-6.

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Synthesis Using Allylidenedihydropyridines. 3.[1] Synthesis and Thermolysis of Functionalized 2-Allylidene-1,2-dihydropyridines

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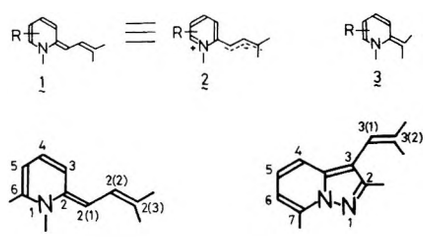
Some 2-allylidene-1,2-dihydropyridines (**19–24**) possessing an electrophilic center in the 1-substituent were prepared by the reactions of pyridinium salts **10, 13,** and **14** with ethoxymethylene compounds **17** and **18** in the presence of alkali, and they were converted in high yields to the corresponding 3-ethenylpyrazolo[1,5-*a*]pyridines **25, 26,** and **29–32** with elimination of ethyl *N*-methylcarbamate **38** by heating in refluxing xylene. On the other hand, the reactions of pyridinium salts **11** + **12** and **15** with the same reagents, **17** and **18,** did not give the corresponding allylidenedihydropyridines, but directly afforded pyrazolopyridines **27, 28, 33,** and **34** in comparatively high yields.

Although 2-allylidene-1,2-dihydropyridine **1** is a vinylog of 2-methylene-1,2-dihydropyridine **3** which is one of the most important precursors in the indolizine synthesis,[2] its versatility as a source of heterocycles has not been investigated at all. Since this molecule **1** has also the contribution of the ionic



structure **2,** in which the negative charge delocalizes on the 2-allylidene group, its nucleophilic reaction due to this structure **2** would be expected.

Recently, we have reported a simple and widely applicable preparative method for allylidenedihydropyridines[3] and the formation of functionalized 2-allylidene-1,2-dihydropyridines[4] using this route. This paper describes the preparations of some 2-allylidene-1,2-dihydropyridines possessing an electrophilic center and their conversions to 3-ethenylpyrazolo[1,5-*a*]-pyridines.

Results and Discussion

Preparations of Pyridinium Salts 10–16. Pyridinium salts possessing an electrophilic center in the 1-substituent were prepared by the alkylation of various 2-picolinium *N*-ylides which can act not only as 1,3-dipoles but also as 1,5-dipoles:[5] treatment of 1-imidoylimino- (**4–7**),[5h] 1-vinylimino- (**8**), and 1-ethoxycarbonyliminopyridinium ylide (**9**)[5a] with methyl iodide at room temperature afforded the corresponding pyridinium salts **10, 11** + **12,** and **13–16** in quantitative yields, respectively (Scheme I).

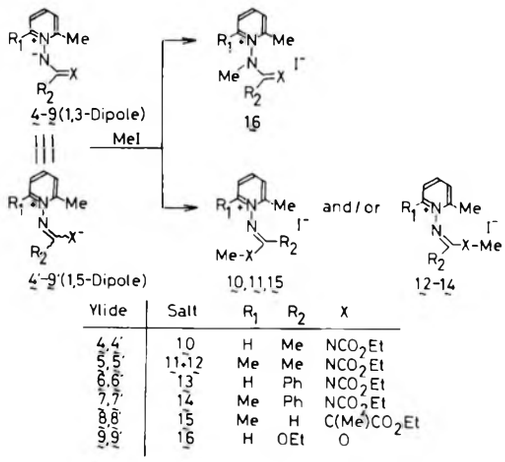
Since the formations of various types of pyridinium salts might be possible via the alkylation, the structures of the resulting pyridinium salts **10–16** were indicated by their NMR spectra (Table I) and the thermal behavior of the corresponding allylidenedihydropyridines derived from the pyri-

Table I. NMR Data of Pyridinium Salts

compd no.	registry no.	C-2	C-3	C-4	C-5	C-6	NMe	R_2	X
10	66270-14-2	2.21 s	8.43 br d	8.69 br t	8.27 br t	9.24 d	3.54 s	2.39, s	4.38 q, 1.40 t
		$J_{3,4} = J_{4,5} = 7.5$, $J_{5,6} = 6.5$, $J_{Et} = 7.0$ Hz							
11	66270-15-3	2.70 s	8.18 d	8.35 t	8.18 d	2.70 s	3.60 s	2.27 s	4.38 q, 1.40 t
		$J_{3,4} = J_{4,5} = 7.5$, $J_{Et} = 7.0$ Hz							
12	66270-16-4	2.77 s	8.02 d	8.44 t	8.02 d	2.77 s	3.28 s	2.27 s	3.99 q, 1.12 t
		$J_{3,4} = J_{4,5} = 7.5$, $J_{Et} = 7.0$ Hz							
13	66270-17-5	2.80 s	*a*	8.42 br t	*a*	9.49 d	3.28 s	7.5–8.2 m	3.98 q, 1.07 t
		$J_{3,4} = J_{4,5} = 7.5$, $J_{5,6} = 6.5$, $J_{Et} = 7.0$ Hz							
14	66270-18-6	2.81 s	8.15 d	8.42 q	8.15 d	2.81 s	3.07 s	7.5–8.0 m	4.03 q, 1.05 t
		$J_{3,4} = 7.5$, $J_{4,5} = 7.0$, $J_{Et} = 7.0$ Hz							
15	66270-19-7	2.80 s	8.17 d	8.53 q	8.17 d	2.80 s	1.67[b] s	7.74 s	4.35 q, 1.33 t
		$J_{3,4} = 7.5$, $J_{4,5} = 7.0$, $J_{Et} = 7.0$ Hz							
16	66270-20-0	2.91 s	8.36 br d	8.77 br t	8.23 br t	9.66 d	3.82 s		4.34 q, 1.32 t
		$J_{3,4} = J_{4,5} = 7.5$, $J_{5,6} = 6.5$, $J_{Et} = 7.0$ Hz							

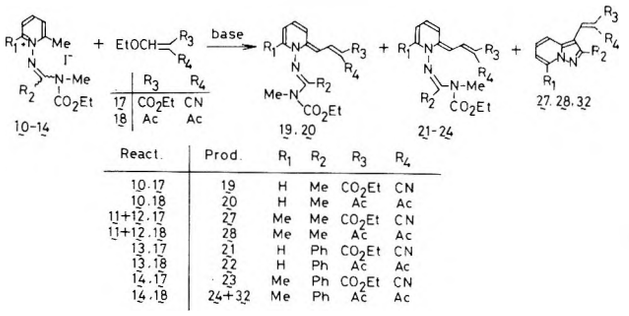
[a] Overlapped with the phenyl signals at δ 7.5–8.2. [b] C-methyl proton.

Scheme I



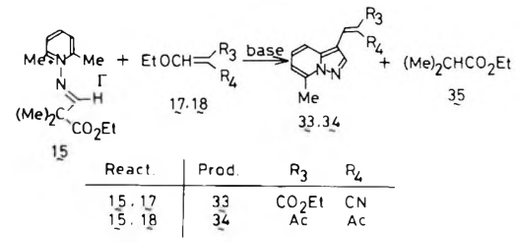
Ylide	Salt	R_1	R_2	X
4,4'	10	H	Me	NCO_2Et
5,5'	11+12	Me	Me	NCO_2Et
6,6'	13	H	Ph	NCO_2Et
7,7'	14	Me	Ph	NCO_2Et
8,8'	15	Me	H	$C(Me)CO_2Et$
9,9'	16	H	OEt	O

Scheme II



React.	Prod.	R_1	R_2	R_3	R_4
10,17	19	H	Me	CO_2Et	CN
10,18	20	H	Me	Ac	Ac
11+12,17	27	Me	Me	CO_2Et	CN
11+12,18	28	Me	Me	Ac	Ac
13,17	21	H	Ph	CO_2Et	CN
13,18	22	H	Ph	Ac	Ac
14,17	23	Me	Ph	CO_2Et	CN
14,18	24+32	Me	Ph	Ac	Ac

Scheme III



React.	Prod.	R_3	R_4
15,17	33	CO_2Et	CN
15,18	34	Ac	Ac

dinium salts. Inspection of the structures using Dreiding models indicated that free rotation about the nitrogen–nitrogen single bond is strongly restricted by the 2- (or 2,6-) methyl group in the 1-pyridyl moiety and, hence, in molecules such as salts **12–14** the influence of the diamagnetic ring current due to the 1-pyridyl group is seen on the *N*-ethoxycarbonyl and the *N*-methyl groups. The NMR spectrum of the salt mixture **11** + **12** obtained from *N*-ylide **5** and methyl iodide, for example, showed each pair of proton signals at δ 1.12 and 1.40 (each 3 H, t, J = 7.0 Hz) and 3.99 and 4.38 (each 2 H, q, J = 7.0 Hz) due to the *N*-ethoxycarbonyl groups, and at δ 3.28 and 3.60 (each 3 H, s) due to the *N*-methyl groups. The signals at δ 1.12, 3.99, and 3.28, at higher magnetic field, should correspond to those of salt **12**, only in which the shielding effect due to the 1-pyridyl group can be expected. The ratio of salt **11** to **12** was determined to be about 2:1 by the integrations of the proton peaks of each *N*-methyl group. Furthermore, the NMR spectrum of salt **15** derived from ylide **8** exhibited proton signals at δ 1.33 (3 H, t, J = 7.0 Hz) and 4.35 (2 H, q, J = 7.0 Hz) due to the ethoxycarbonyl group and at δ 1.67 (6 H, s) and 7.74 (1 H, s) due to the two methyl and the imino methine groups, together with signals at δ 2.80 (6 H, s), 8.17 (2 H, almost d, J = 7.5 and 8.5 Hz), and 8.53 (1 H, q, J = 7.5 and 8.5 Hz) attributable to the 2,6-lutidine moiety. The chemical shift (δ 1.67) of the methyl group from the alkylating agent indicated clearly that salt **15** is not the N-methylated product but the C-methylated one, and those (δ 1.33 and 4.35) of the ethoxycarbonyl group indicated also that a shielding effect upon this group is not apparent. The structures of other salts **10**, **13**, **14**, and **16** were determined similarly.

The methylated position in salts **10–15** was also confirmed by the elimination of ethyl isobutyrate or ethyl *N*-methylcarbamate from the corresponding allylidenedihydropyridines (see below).

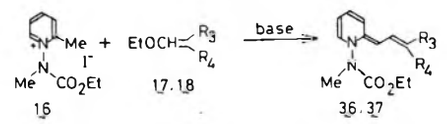
Reactions of Pyridinium Salts 10–16 with Ethoxymethylene Compounds 17 and 18. The reactions of pyridinium salts **10**, **13**, and **14** with activated ethoxymethylene compounds such as ethyl ethoxymethylenecyanoacetate (**17**) and 3-ethoxymethylenepentane-2,4-dione (**18**) in the presence of alkali gave the expected 2-allylidene-1,2-dihydropyridine derivatives **19–24** as reddish crystals in yields of 50–87%, while those of salts **11** + **12** and **15** with the same reagents did not afford such allylidenedihydropyridines but gave the corresponding 3-ethenylpyrazolo[1,5-*a*]pyridine derivatives **27**, **28**, **33**, and **34** as yellow or pale yellow crystals in yields of 56–72%. In the reaction of salt **14** with **18** pyrazolopyridine **32** was also isolated in 24% yield together with allylidenedihydropyridine **24** (50%). In the reactions of **15** with **17** and **18**, the formation of ethyl isobutyrate **35** was detected by GLC of the reaction mixtures. Similarly, the reactions of salt **16** with **17** and **18** gave the corresponding allylidenedihydropyridines **36** and **37** in 63 and 88% yields. These results are shown in Schemes II–IV.

Table II. NMR Data of Allylidenedihydropyridines

compd no.	registry no.	C-3	C-4	C-5	C-6	2(1)	2(2)	NMe	R_2	Et		$R_{3,4}$	
19	66270-21-1	7.66 br d	7.39 br t	6.51 br t	7.24 br d	5.56 d	8.32 d	3.56 s	2.25 s	4.38 q	4.31 q	1.37 t	1.30 t
		$J_{3,4}$ = 8.0,	$J_{4,5}$ = $J_{5,6}$ = 7.5,	$J_{2(1),2(2)}$ = 13.0,	J_{Et} = 7.0 Hz								
20	66270-22-2	7.4 br d	7.39 br t	6.57 br t	7.25 d	6.98 d	8.06 d	3.66 s	2.26 s	4.36 q	1.37 t	2.43[a] s	
		$J_{3,4}$ = 8.0,	$J_{4,5}$ = $J_{5,6}$ = 7.5,	$J_{2(1),2(2)}$ = 13.5,	J_{Et} = 7.0 Hz								
21	66270-23-3	b	b	6.51 br t	b	5.77 d	8.37 d	2.98 s	7.2–8.1 m	4.14 q	1.02 t	4.29 q	1.30 t
		$J_{4,5}$ = $J_{5,6}$ = 7.5,	$J_{2(1),2(2)}$ = 13.0,	J_{Et} = 7.0 Hz									
22	66270-24-4	b	b	6.52 br t	b	6.94 d	8.09 d	3.00 s	7.2–8.1 m	4.13 q	1.03 t	2.38[a] s	
		$J_{4,5}$ = $J_{5,6}$ = 7.5,	$J_{2(1),2(2)}$ = 13.5,	J_{Et} = 7.0 Hz									
23	66270-25-5	c	c	6.52 br d	2.42 s	5.63 d	8.30 d	3.02 s	7.1–8.1 m	4.08 q	1.06 t	4.27 q	1.29 t
		$J_{4,5}$ = 7.5,	$J_{2(1),2(2)}$ = 13.0,	J_{Et} = 7.0 Hz									
24	66270-26-6	d	d	6.49 br d	2.41 s	7.13 d	7.97 d	2.93 s	7.2–8.0 m	4.02 q	1.08 t	2.38[a] s	
		$J_{4,5}$ = 7.0,	$J_{2(1),2(2)}$ = 13.0,	J_{Et} = 7.0 Hz									
36	66270-27-7	7.54 br d	7.17 br t	6.34 br t	7.21 br d	5.57 d	8.35 d	3.39 s		4.37 q	4.34 q	1.31 t	1.30 t
		$J_{3,4}$ = 8.0,	$J_{4,5}$ = $J_{5,6}$ = 7.5,	$J_{2(1),2(2)}$ = 13.0,	J_{Et} = 7.0 Hz								
37	66270-28-8	7.55 br d	7.17 br t	6.29 br t	7.20 br d	6.48 br d	8.00 d	3.39 s		4.37 q	1.28 t	2.44 s	2.42 s
		$J_{3,4}$ = 8.0,	$J_{4,5}$ = $J_{5,6}$ = 7.0,	$J_{2(1),2(2)}$ = 13.5,	J_{Et} = 7.0 Hz								

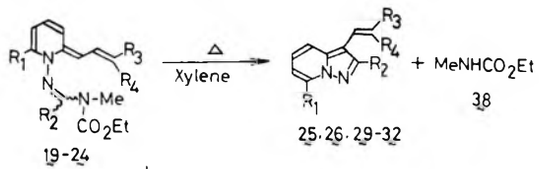
[a] 6 H of the two acetyl groups. [b] Overlapped with the phenyl signals at δ 7.2–8.1. [c] Overlapped with the phenyl signals at δ 7.1–8.1. [d] Overlapped with the phenyl signals at δ 7.2–8.0.

Scheme IV



React.	Prod.	R_3	R_4
16,17	36	CO_2Et	CN
16,18	37	Ac	Ac

Scheme V



React.	Prod.	R_1	R_2	R_3	R_4
19	25	H	Me	CO_2Et	CN
20	26	H	Me	Ac	Ac
21	29	H	Ph	CO_2Et	CN
22	30	H	Ph	Ac	Ac
23	31	Me	Ph	CO_2Et	CN
24	32	Me	Ph	Ac	Ac

These allylidenedihydropyridines **19–22, 36,** and **37** were comparatively stable under ordinary conditions but **23** and **24** were unstable and decomposed gradually even at room temperature.[6]

The structures of allylidenedihydropyridines **19–24, 36,** and **37** were determined by the analyses of their physical and spectral data and by the comparisons of their NMR spectra (Table II) with those of other allylidenedihydropyridines prepared earlier by us[3] and other investigators.[7] The stereochemistry of the 1-substituent in compounds **19–24** was also assigned by similar inspection of their NMR spectra as described in pyridinium salts **10–15,** and that of the 2-allylidene group in **19–24, 36,** and **37** was determined by the analyses of the chemical shifts of each 2(2) proton and by the recent literature.[7c] For example, the *N*-methyl signals appeared at near δ 3.6 (**19** and **20**) or 3.0 (**21–24**) and the *N*-ethoxycarbonyl signals at near δ 4.4 and 1.4 (**19** and **20**) or 4.1 and 1.1 (**21–24**) in the NMR spectra. Of course, the signals (near δ 3.0, 4.1, and 1.1) appearing at a higher region must be those of the *N*-ethoxycarbonyl-*N*-methylamino group cis to the 1-(2-allylidene-1,2-dihydropyridyl) group as proposed for the structures of **21–24** (see Scheme II). On the other hand, the *N*-methyl signals of **36** and **37** both appeared at δ 3.39.

The stereochemistry of the ethoxycarbonyl and the cyano groups in the 2-allylidene moiety of **19, 21, 23,** and **36** was determined by the comparison of their chemical shifts (near δ 8.3) of the 2(2) protons with those (near δ 8.0) of diacetyl derivatives **20, 22, 24,** and **37,** because the extent of diamagnetic anisotropy in such circumstance decreases usually in order of ester, acyl, and cyano groups. The other chemical shifts of the allylidene and the dihydropyridine moieties were quite parallel to those of known allylidenedihydropyridines reported recently by us.[3] The other products, 3-ethenylpyrazolo[1,5-*a*]pyridines **27, 28,** and **32–34,** will be discussed in the next section.

Thermolyses of Allylidenedihydropyridines 19–24, 36, and 37. In order to confirm the formation mechanism of 3-ethenylpyrazolo[1,5-*a*]pyridines **27, 28,** and **32–34** and to clarify the reactivity of these functionalized allylidenedihydropyridines we examined the thermolyses of **19–24, 36,** and **37** isolated in the above reactions. When solutions of allylidenedihydropyridines **19–24** and xylene were heated at the reflux temperature for 3–6 h, the red color of the reaction solutions faded gradually and in each case two new spots were

Table III. NMR Data of 3-Ethenylpyrazolo[1,5-*a*]pyridines

compd no.	registry no.	C-4	C-5	C-6	C-7	3(1)	R_2	R_3[a] and R_4	
25	66270-04-0	8.47 d	7.58 br t	7.16 br t	8.66 d	8.52 s	2.63 s	4.47 q	1.42 t
		$J_{4,5}$ = 8.0, $J_{5,6}$ = 7.5, $J_{6,7}$ = 7.0 Hz							
26	66270-05-1	7.48 m	7.48 m	7.02 m	8.61 d	8.00 s	2.55 s	2.46 s	2.30 s
		$J_{4,5}$ = 0, $J_{6,7}$ = 7.5 Hz							
27	66270-06-2	8.17 d	7.44 q	6.87 d	2.78 s	8.35 s	2.61 s	4.41 q	1.39 t
		$J_{4,5}$ = 8.0, $J_{5,6}$ = 7.5 Hz							
28	66270-07-3	7.26 d	7.26 d	6.74 t	2.76 s	7.87 s	2.53 s	2.41 s	2.25 s
		$J_{4,5}$ = 0, $J_{4,6}$ = $J_{5,6}$ = 4.0 Hz							
29	66270-08-4	8.42 d	*b*	7.26 br t	8.86 d	8.57 s	7.5–7.8 m	4.46 q	1.37 t
		$J_{4,5}$ = 9.0, $J_{5,6}$ = 7.5, $J_{6,7}$ = 7.0 Hz							
30	66270-09-5	*c*	7.27 br t	6.89 br t	8.49 d	7.81 s	7.4–7.8 m	2.38 s	2.22 s
		$J_{4,5}$ = 9.0, $J_{5,6}$ = 7.5, $J_{6,7}$ = 7.0 Hz							
31	66270-10-8	8.33 d	*d*	7.08 br d	2.91 s	8.60 s	7.5–7.9 m	4.46 q	1.39 t
		$J_{4,5}$ = 9.0, $J_{5,6}$ = 7.5 Hz							
32	66270-11-9	*e*	*e*	6.84 br d	2.83 s	7.92 s	7.3–7.9 m	2.38 s	2.21 s
		$J_{5,6}$ = 7.5 Hz							
33	66270-12-0	7.72 dd	7.44 q	6.90 br d	2.95 s	8.39 s	9.07 s	4.43 q	1.51 t
		$J_{4,5}$ = 9.0, $J_{5,6}$ = 7.5, $J_{4,6}$ = 1.5 Hz							
34	66270-13-1	7.64 d	7.36 q	6.84 br d	2.79 s	7.64 s	8.17 s	2.45[f] s	
		$J_{4,5}$ = 9.0, $J_{5,6}$ = 7.0 Hz							

[a] When R_3 = CO_2Et, J_{Et} = 7.0 Hz. [b] Overlapped with the phenyl signals at δ 7.5–7.8. [c] Overlapped with the phenyl signals at δ 7.4–7.8. [d] Overlapped with the phenyl signals at δ 7.5–7.9. [e] Overlapped with the phenyl signals at δ 7.3–7.9. [f] 6 H of the two acetyl groups.

Table IV. Some Data of the Reactions of Salts with Ethylenes

materials no.		prod. no. (%)[a]	appearance	mp, °C	ν_{CO} (KBr)	ν_{CN} (KBr)
10	**17**	**19** (87)	red prisms	96–98 dec	1729, 1669	2215
10	**18**	**20** (78)	red prisms	117–119 dec	1734	
11 + 12	**17**	**27** (72)	yellow needles	114–116	1717	2240
11 + 12	**18**	**28** (72)	yellow needles	120–122	1696, 1644	
13	**17**	**21** (84)	red prisms	130–132 dec	1731, 1680	2220
13	**18**	**22** (74)	red prisms	136–138 dec	1726	
14	**17**	**23** (77)	red prisms	110–112 dec	1726, 1672	2220
14	**18**	**24** (50)[b]	red prisms		1726	
		32 (24)	yellow needles	102–104	1675	
15	**17**	**33** (47)	pale yellow needles	150–153	1711	2235
15	**18**	**34** (56)	pale yellow needles	159–161	1701	
16	**17**	**36** (63)	red prisms	170–171	1707	2230
16	**18**	**37**(88)	red prisms	158–160	1713	

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds except **24**. [b] Recrystallization of **24** was unsuccessful because of its unstability.

observed by TLC. From the reaction mixtures the corresponding 3-ethenylpyrazolo[1,5-*a*]pyridine derivatives **25, 26,** and **29–32** were isolated in 82–96% yields, and ethyl *N*-methylcarbamate **38** was also detected (by GLC). On the other hand, the thermolyses of **36** and **37** did not give the expected pyrazolopyridinone derivatives but afforded only intractable tarry substances (Scheme V).

The structural assignments of 3-ethenylpyrazolo[1,5-*a*]-pyridine derivatives **25–34,** which were prepared from allylidenedihydropyridines **19–24** and directly from the reactions of pyridinium salts **11 + 12** and **15** with ethoxymethylene compounds **17** and **18,** were based upon their physical and spectral properties and by mechanistic consideration of these reactions. The elementary analyses were in good accord with the compositions for the proposed structures, and the NMR spectra (Table III) exhibited aromatic proton signals at δ 6.84–8.86 due to the pyridine moiety and singlet signals at δ 7.64–8.60 due to the vinyl protons. Interestingly, no coupling between the 4 and 5 protons was observed in the NMR spectra of compounds **26** and **28.** Furthermore, the fact that these 3-ethenylpyrazolopyridines **25–34** were formed with the elimination of ethyl isobutyrate **35** or ethyl *N*-methylcarbamate **38** is good evidence for the proposed structures.

Reaction Mechanism. Since allylidenedihydropyridines **19–24** were actually converted to the corresponding 3-ethenylpyrazolopyridines **25, 26,** and **29–32,** the intermediacy of the corresponding allylidenedihydropyridines in the formations of other pyrazolopyridines **27, 28,** and **32–34** is certain. Perhaps, these 3-ethenylpyrazolopyridines **25–34** must be formed by the intramolecular cyclization–eliminations of the corresponding allylidenedihydropyridines.

On the other hand, the failure to isolate the corresponding allylidenedihydropyridines derived from salts **11 + 12** and **15** and the instability of the 6-methyl isomers **23** and **24** seem to indicate acceleration of these cyclizations due to the increase (R_1 = Me) of steric hindrance, and in the case from **15** its decrease (R_2 = H) may also accelerate such cyclization.

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 Elemental Analyzer. The NMR spectra were determined with a JEOL JNM-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO DS-301 spectrophotometer.

Preparations of Pyridinium Salts 10–16. Pyridinium salts **10–16**

Table V. Preparations and Some Data of Pyrazolopyridines

material no.	prod. no. (%)[a]	appearance	mp, °C	ν_{CO} (KBr)	ν_{CN} (KBr)
19	**25** (96)	yellow needles	102–103	1716	2240
20	**26** (93)	yellow needles	91–93	1675	
21	**29** (96)	yellow needles	190–192	1716	2240
22	**30** (92)[b]	yellow amorph		1685[c]	
23	**31** (96)	yellow needles	159–162	1713	2240
24	**32** (82)	yellow needles	102–104	1675	
36	(0)	no reaction			
37	(0)	decomposition			

[a] Satisfactory analyses were reported for compounds **25, 26, 29** and **31**. [b] Crystallization of **30** was unsuccessful. [c] Neat.

were prepared in quantitative yields by the reactions of pyridinium *N*-ylides **4–9**[5a,h,8] with methyl iodide in chloroform or without solvent at room temperature. These salts **10–16** were used for the next reactions without further purification because of the difficulty of their crystallization. The NMR data of salts **10–16** are listed in Table I.

Reactions of Pyridinium Salts 10–16 with Ethoxymethylene Compounds 17 and 18. General method: A solution of pyridinium salt (2.1 mmol) and ethyl ethoxymethylenecyanoacetate **17** (0.34 g, 2 mmol) or 3-ethoxymethylenepentane-2,4-dione **18** (0.31 g, 2 mmol) in chloroform (50 mL) was treated with potassium carbonate (5 g) at room temperature for 3–4 days. The reaction mixture was then filtered to remove insoluble inorganic substances and the filtrate was concentrated in vacuo. The residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Pyrazolopyridines **27, 28,** and **32–34** were isolated from the ether layer and allylidenedihydropyridines **19–24, 36,** and **37** from the chloroform layer. Recrystallizations of pyrazolopyridines **27, 28,** and **32–34** and allylidenedihydropyridines **19–23, 36,** and **37** were carried out from ether–hexane and chloroform–hexane, respectively. However, the preparation of the analytical sample of **24** was unsuccessful because **24** decomposed gradually even at room temperature to give pyrazolopyridine **32** and ethyl *N*-methylcarbamate **38**. Furthermore, ethyl isobutyrate **35** or ethyl *N*-methylcarbamate **38** was detected by GLC of the reaction solutions. These results and some physical data are shown in Tables II–IV.

Thermolyses of Allylidenedihydropyridines 19–24, 36, and 37. General method: A solution of 2-allylidenedihydropyridine (1 mmol) in xylene (50 mL) was heated at the reflux temperature until the disappearance of the starting material was observed by TLC (about 3–6 h). The reaction solution was concentrated in vacuo, and the residue was separated in the usual manner. Recrystallization from ether–hexane gave the corresponding 3-ethenylpyrazolopyridines **25, 26,** and **29–32**. The formation of ethyl *N*-methylcarbamate **38** was also confirmed by GLC of the reaction solutions. On the other hand, the thermolyses of allylidenedihydropyridines **36** and **37** did not give the expected pyrazolopyridinones but afforded only tarry substances. These results and some physical data are listed in Tables III and V.

Acknowledgment. The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education (No. 265251).

Registry No.—**4,** 60705-40-0; **5,** 60705-41-1; **6,** 60705-42-2; **7,** 60705-43-3; **8,** 66303-83-1; **9,** 22928-83-2; **17,** 94-05-3; **18,** 33884-41-2.

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(6) Compounds **23** and **24** were gradually converted to 3-ethenylpyrazolo[1,5-a]pyridines **31** and **32**, respectively.
(7) (a) T. Severin and H.-J. Böhme, *Chem. Ber.*, **101**, 2925 (1968); (b) R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1*, 744 (1975); (c) J. Kuthan, D. Ilavsky, J. Krechel, and P. Trska, *Tetrahedron Lett.*, 4763 (1976).
(8) *N*-Vinyliminopyridinium ylide **8**, red prisms, mp 131–134 °C, ν(KBr) 1535 cm^{-1} (CO) (Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.72; H, 7.70; N, 12.11) was prepared in 84% yield by the reaction of 1-aminopyridinium iodide with ethyl β-bromomethacrylate according to the Sasaki's procedure. See ref 5e.

Teleamination of the Imidazo[1,2-*a*]pyridine System

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The reaction of 3-bromoimidazo[1,2-*a*]pyridine (**2**) with strong bases leads to metal–halogen and alkyl–halogen (coupling) exchange at the 3 position of the imidazole ring with CH_3Li, but leads to debromination, coupling via the 5 position (to give the dehydrodimer **11**), and telesubstitution at *all* positions of the pyridinoid ring with metal amides. Which products are obtained depends on the amide used. The formation of the amination products is interpreted to proceed by attack at positions 5 and/or 7, followed by migration to adjacent positions via an aziridine intermediate. Only the first step of the established ANRORC (addition–nucleophilic–ring opening–ring closing) mechanism of other teleamination reactions can be retained for these reactions, subsequent steps including ring opening and ring closing, but in the reverse sequence. A bromination product, the formation of which implicates a positive bromine species, and a Chichibabin amination product are also formed. The coupling product **11** is obtained when the parent imidazo[1,2-*a*]pyridine (**1**) is treated with KNH_2.

Imidazo[1,2-*a*]pyridine (**1**) contains both the π-excessive imidazole and the π-deficient pyridine rings. As such it is expected to undergo reactions of both types of molecules. The anticipated higher electron density in the five-membered ring is confirmed by frontier[1] and CNDO/2[2] calculations and is amply demonstrated by experimental evidence of electrophilic substitution at the 3 position.[3] When this position is blocked, electrophilic substitutions generally fail.[4] Much less is known about the reactivity of imidazo[1,2-*a*]pyridines toward nucleophiles. The parent compound **1** undergoes hydrogen–

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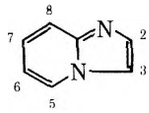
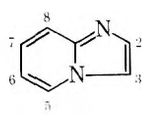
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) of Some Imidazo[1,2-*a*]pyridines[a]



Substituent	Compd no.	Registry no.	H_2	H_3	H_5	H_6	H_7	H_8	$COCH_3$	CH_2	CH_3
None	1[b]	274-76-0	7.58	7.63	8.05	6.78	7.16	7.62			
3-Br	2	4926-47-0	7.67		8.19	6.95	7.25	7.67			
3-CH_3	3	5857-45-4	7.43		7.89	6.79	7.12	7.64			2.46
2-CH_3		934-37-2		7.29	7.99	6.63	7.03	7.48			2.40
6-Br, 7-NHEt	5	66358-04-1	7.41	7.28	8.19			6.57		3.16	1.37
6-Br	33	6188-23-4	7.68	7.60	8.32		7.20	7.59			
8-NEt_2	7	66358-05-2	7.58	7.51	7.70	6.66	6.28			3.76	1.17
7-NEt_2	8	66358-06-3	7.37	7.26	7.83	6.38		6.51		3.33	1.15
5-NEt_2	9	66358-07-4	7.66	7.66		6.35	7.18	7.44		3.20	1.10
5,7-diNEt_2	10	66358-08-5	7.40	7.33		5.98		6.44		3.40	1.22
										3.19	1.13
None	1[c]		7.98	7.64	8.59	6.88	7.22	7.62			
2-$NHCOCH_3$	19	38922-76-8		8.40	8.80	7.12	7.48	7.70	2.40		
3-$NHCOCH_3$	20	66358-09-6	7.85		8.46	7.26	7.56	7.91	2.50		
5-$NHCOCH_3$	17	66358-10-9	7.96	7.65		7.09	7.28	7.47	2.22		
6-$NHCOCH_3$	14	66358-11-0	8.00	7.54	9.22		7.15	7.55	2.09		
8-$NHCOCH_3$	18	66358-12-1	7.95	7.56	8.24	6.84	7.99		2.22		
5-CH_3		933-69-7	7.89	7.78		6.78	7.23	7.60			2.67
5-R[d,e]	11	66358-13-2	7.67	7.21		7.35	7.47	7.89			
3-NO_2		4926-45-8	8.84		9.45	7.53	7.83	8.05			
3-NO_2, 5-CH_3	31	34165-08-7	8.79			7.35	7.85[f]	7.85[f]			2.70
3-NO_2, 5(3′-NO_2)R[d,e]	25	66358-14-3	8.94			7.89	8.07	8.24			
3-NO_2, 5(3′-NO_2, 7′-$NHCOCH_3$)R[d]	27	66358-15-4	8.83 8.73			7.81 7.74	7.98	8.16 8.32	2.16		
3-NO_2,8-$NHCOCH_3$	32	66358-16-5	8.71		9.00	7.40	8.40		2.23		

[a] Assignments of chemical shifts are based not only on similarity to those of analogous compounds but primarily on the splitting patterns. Typical values of coupling constants are: $J_{2,3} \sim 1.2$, $J_{3,8} \sim 0.5$, $J_{5,6} = 6$–7.5, $J_{5,7} = 0$–2, $J_{5,8} = 0$–1, $J_{6,7} = 6.5$–7.5, $J_{6,8} = 1.5$–2.5, $J_{7,8} = 8.5$–9.5 Hz. Although the H_3 signal tends to be broader than that due to H_2, assignments to H_2 and H_3 may be inverted in some cases. [b] Data in the upper part of table are of dilute $CDCl_3$ solutions. [c] Data in the lower part of the table are of dilute Me_2SO-d_6 solutions. [d] R = 5′-imidazo[1,2-*a*]pyridyl. [e] Chemical shifts obtained from simulated spectra. [f] Center of overlapping multiplets.

deuterium exchange in the presence of NaOD at positions 3 and 5 via the corresponding anions generated by proton ab-



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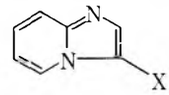
straction.[5] Phenyllithium also abstracts hydrogen at the 3 position.[6] While attempts to displace bromine at the 3 position with various nucleophiles (CH_3O^-, morpholine, and piperidine) have failed, electrophilic displacement with SeO_2 has been achieved.[7] Reaction of alkoxide with either the 2- or the 7-chloro derivative is reported to be unsuccessful. However, a 5-chloro substituent can be displaced.[8] In a rare example of nucleophilic substitution at the 2 position,[9] substitution is facilitated by the presence of the highly activating NO_2 group in the 3 position. We have recently shown that nucleophilic attack can occur at C_2 or C_3 when N_1 carries an appropriate leaving group (Cl, Br,[10] $OPOCl_2$,[11] and OCH_3[12]). We report now the results of some further reactions with strong nucleophiles[13] (CH_3Li, KNH_2, EtNHLi, and Et_2NLi).

When a mixture of 3-bromoimidazo[1,2-*a*]pyridine (**2**) and

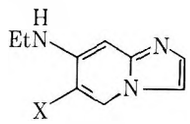


2, X = Br
3, X = CH_3
4, X = NO_2

methyllithium in ether is stirred for 45 min at 0 °C, debromination with concomitant formation of approximately equal amounts of the parent compound **1** and its 3-methyl derivative (**3**) occurs. These compounds were identified by comparison of properties of solid derivatives, the nitration product **4** of the parent compound **1** and the picrate of compound **3**, with those of authentic samples (see Table I for ^{1}H NMR spectral data). The reaction mixture consisted of at least 90% of these materials, since its ^{1}H NMR spectrum was almost the same[14] as that of a 1:1 mixture prepared from pure authentic compounds. Even small amounts of the possible 2-methyl derivative, if formed, would have been detectable by ^{1}H NMR spectroscopy since its H_3 signal appears as a sharp singlet in a region relatively free of other absorption.

Use of the aprotic solvent, ether, and strong anion base thus leads only to bromine–lithium exchange[15] and coupling.[16] Mechanisms for these types of reactions have been discussed.[17]

The reactions of 3-bromoimidazo[1,2-*a*]pyridine (**2**) with the amine anions lead to complex mixtures containing considerable amounts of tar. The major product (35%) from lithium ethylamide in 20% ethylamine/ether is the parent compound **1**. This reductive dehalogenation[18] evidently occurs by abstraction of Br^+ since a minor product (2.5%) is 6-bromo-7-ethylaminoimidazo[1,2-*a*]pyridine (**5**). The formation of this compound is readily explicable only by postulating

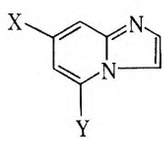


5, X = Br
6, X = H

electrophilic substitution at position 6 of 7-ethylaminoimidazo[1,2-*a*]pyridine (**6**), which in turn is formed by telesubstitution of bromine in compound **2** (vide infra). The structures of the bromo compound **5** and of most of the other new compounds were established by analysis of mass and ^{1}H NMR (see Table I) spectra and elemental composition.[19]

From the complex mixture of products of the reaction with lithium diethylamide in 30% Et_2NH/12% hexane/Et_2O, the parent compound **1** (10%) as well as the four substitution products, **7–10**, could be isolated.[20] It should be noted that the

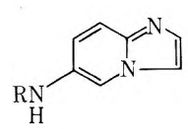
7 (9%)



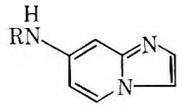
8, X = Et_2N; Y = H (13%)
9, X = H; Y = Et_2N (4%)
10, X = Y = Et_2N (1%)

7-diethylamino derivative **8** is formed in highest yield. The formation of the disubstituted product **10** can be attributed to a Chichibabin reaction of compound **8**.

When the reaction was carried out with potassium amide in 55% NH_3/ether, the parent compound **1** (ca. 10%), a dehydrodimer (**11**) of compound **1**, an amino derivative (**12**) of the dehydrodimer (vide infra), and 6-aminoimidazo[1,2-*a*]pyridine (**13**, 50%) could be isolated. The 7-amino derivative **15** (<1%) is believed to be formed also. These materials were separated and identified as acetamido derivatives.

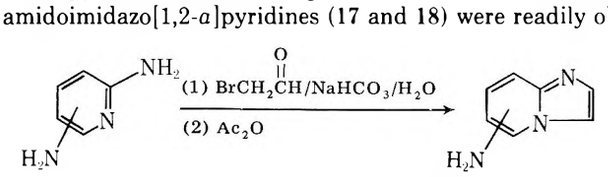


13, R = H
14, R = $COCH_3$



15, R = H
16, R = $COCH_3$

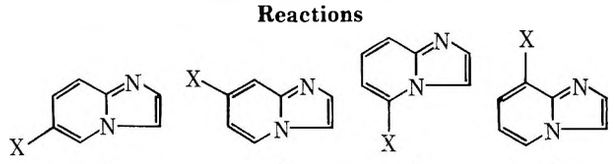
The structure of the acetamido compound (**14**) was confirmed by an unequivocal synthesis from 2,5-diaminopyridine and bromoacetaldehyde, followed by acetylation. Attempts to prepare compound **15** by similar condensation of 2,4-diaminopyridine failed, although both the 5- and the 8-acetamidoimidazo[1,2-*a*]pyridines (**17** and **18**) were readily obtained from the corresponding diaminopyridines. The remaining 2- and 3-acetamido isomers **19**[21] and **20**[9] were prepared by known procedures. TLC comparisons of the acetylated amination mixtures and the five authentic acetamido compounds showed unequivocally that *none* of either the 8- or the 3-acetamido compound was present. A component with the same R_f value as 2-acetamidoimidazo[1,2-*a*]pyridine (**19**) was formed in minute amount (<0.1%). Structure **16** is tentatively assigned to the acetyl derivative of compound **15** since it showed a mass spectral fragmentation pattern very similar to those of the other acetamido derivatives, but its melting point and IR spectrum differed from those of the other five isomers (**14**, **17–20**).



14, 6-$NHCOCH_3$
17, 5-$NHCOCH_3$
18, 8-$NHCOCH_3$

While no definitive statement can be made regarding the mechanism of the teleamination reactions, the substitution patterns in the isolated products (see Table II) nevertheless establish a trend which is consistent with the following mechanism (see Scheme I).

Table II. Isomer Distribution (%) in the Amination Reactions

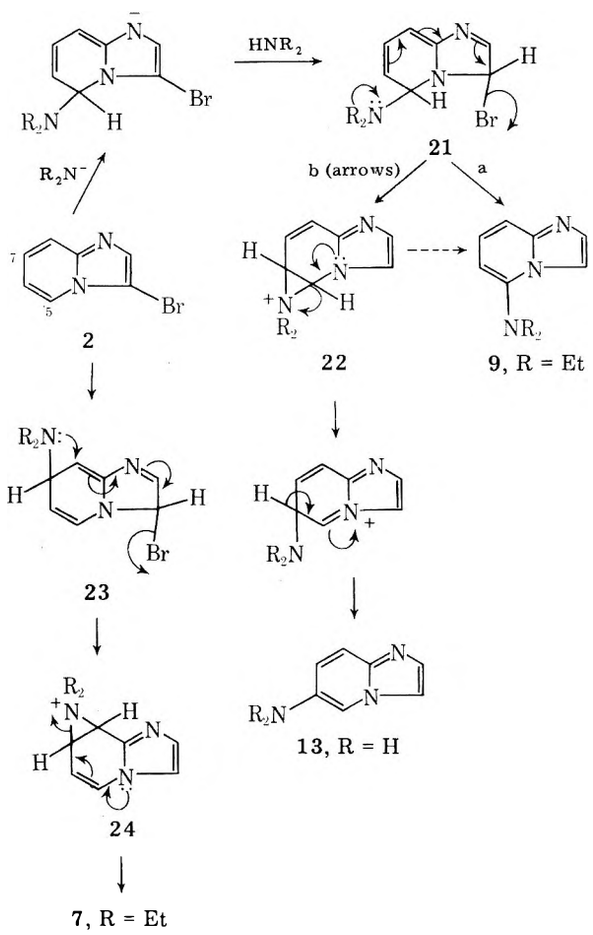


X	A	B	C	D
NH_2	50	Trace	?	
NHEt	?	2.5[a]	?	?
NEt_2	?	13	4	9

[a] Isolated as the 6-bromo derivative.

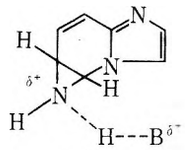
Attack by amide ion preferentially occurs at C_5 (and/or C_7) since in the resulting intermediate the negative charge can be accommodated by nitrogen. A factor contributing to the driving force may well be complexation of the metal ion, K^+ or Li^+, with N_1 in the neutral molecule (**2**). Subsequent or concomitant reaction with the protic amines gives the intermediate **21** from which elimination could occur by two different paths. While path a leads to direct rearomatization of the ring system, it is not necessarily involved in the formation of compound **9**. The high effective concentration of the attacking nucleophile (the NR_2 group in **21**), loss of Br^-, and aromatization of the five-membered ring can all contribute to the driving force for the formation of intermediate **22**. The 5-substituted product (**9**) can then be obtained by loss of H_5 and cleavage of the aziridine ring. However, preferential for-

Scheme I



mation of the 6-substituted product (**13**) is expected if cleavage of the three-membered ring is facilitated by neighboring group participation of N_4. Similar reaction sequences with initial attack at C_7 account for the formation of the 7- and 8-substituted products (**8** and **7**, respectively) with $LiNEt_2$. Since in this case both "non"- and "rearranged" products were isolated and since the 8-substituted compound, which should be formed to a *greater* extent from intermediate **24**, is actually obtained in *smaller* amount, the postulate that the two products are formed by two different reaction paths (a and b) receives some support.[34]

The formation of a very high percentage of "rearranged" 6-substituted product in the KNH_2 relative to the $LiNEt_2$ reaction can be attributed to two factors. Proper orientation for bond formation of the electrons on nitrogen should be easier in the intermediate containing the NH_2 group (**21**, R = H) compared to the bulky NEt_2 group. Furthermore, the newly formed intermediate **22** (R = H) almost certainly does not carry a full positive charge as it must where R = NEt_2, since H bonding to the solvents (Et_2O and NH_3, cf. **22a**) or



22a

proton transfer (to NH_2^-) are both possible. Hence the activation energy of intermediate formation should be considerably lower and the reaction proceeds preferentially via path b. Initial attack by NH_2^- at C_5 in preference to C_7 parallels the behavior of other N heterocycles in the Chichibabin reaction.[22] Preferred attack by NEt_2^- at C_7 rather than C_5 is attributed to greater bulkiness of this moiety.

While the position of substitution in the above compounds could be ascertained from their ^1H NMR spectra, this was not the case for the dehydrodimers, **11** and **26**, that were obtained in the potassium amide reaction. The complex second-order spectrum of compound **11** implied unsymmetrical linkage of the two imidazo[1,2-*a*]pyridine units, yet suggested the absence of C_5 protons (normally the most deshielded in this ring system[23]).

Nitration, which always takes place at C_3 in imidazo[1,2-*a*]pyridines, afforded a dinitro compound which however displays a much simpler ^1H NMR spectrum interpretable in terms of the symmetrical structure **25**. Typically, the spectra of nitration products show not only a *general* downfield shift of all of the ^1H NMR signals but also a *profound* downfield shift of the H_2 and H_5 resonance lines.[24] Signals attributable to H_5 are absent in the spectrum of compound **25**; the lowest field signal is a singlet which must be assigned to H_2; and the areas and splitting pattern of the remaining signals can only be due to three protons located at positions 6, 7, and 8. The dehydrodimer must therefore also have the 5,5′ linkage. Strong support for structures **11** and **25** was obtained from computer simulation of these spectra. The values of the chemical shifts and coupling constants used for the simulated spectrum of the dehydrodimer (**11**) are shown in Figure 1 together with the experimentally obtained spectrum.

The ^1H NMR spectrum of the acetamidodehydrodimer (**26**) could only be obtained in TFAA, a solvent in which the chemical shifts of the protons in this ring system are usually very similar, and could not be interpreted. However, nitration of this compound affords a dinitro derivative that is soluble in dimethyl sulfoxide. The ^1H NMR spectrum is in accord with structure **27**. In addition to the pattern observed for the dinitrodehydrodimer **25**, there are a 3-proton singlet (C(O)-CH_3), a one-proton singlet (H-2′), as well as an AB system.

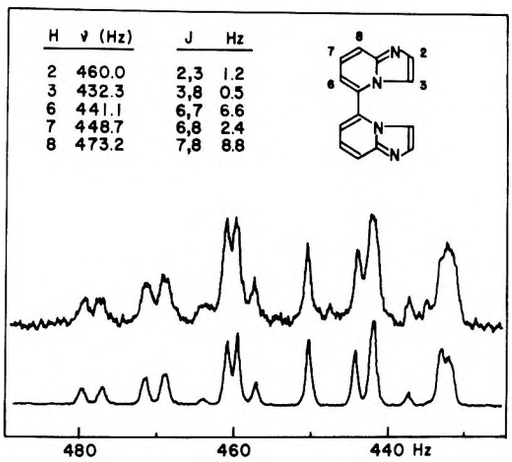
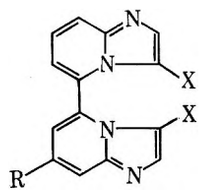


Figure 1. Top line: experimentally observed 60 MHz ^1H NMR spectrum of compound **11** (9mg/0.4 mL Me_2SO-d_6). Bottom line: theoretical spectrum obtained with a Varian Spin Simulation Routine and SS-100 computer system using the frequencies and coupling constants shown (line width = 2, scale factor = 5).

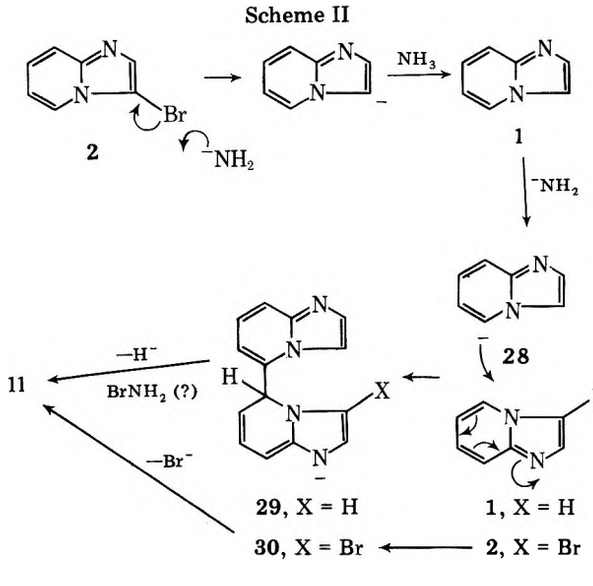


11, R = X = H
12, R = NH_2; X = H
25, R = H; X = NO_2
26, R = CH_3CONH; X = H
27, R = CH_3CONH; X = NO_2

The coupling constant of this pattern (2 Hz) precludes that the two protons are ortho to each other. Therefore, the acetamido group is at C_7′.

The dehydrodimer **11** is most likely formed by the sequence shown in Scheme II. That debromination occurs is shown by the fact that compound **1** was isolated. That proton abstraction at C_5 is reasonable is shown by H/D exchange in aqueous NaOD.[5] Attack of the anion **28** at C_5 of a neutral molecule (**1**) follows the same pattern postulated in the amination reactions. Oxidation of the anion **29**, or its protonation product, should be facile since an aromatic system is formed. Alternatively, reaction of the anion **28** with compound **2** leads to intermediate **30** from which the dehydrodimer **11** can be

Scheme II



formed by prototopic shift and loss of bromide ion. A Chichibabin-type amination of the dehydrodimer **11**, which should occur at C_7 on mechanistic grounds, then gives structure **12**.

Two further experimental findings indicate that the reaction sequence proceeding via intermediate **29** and subsequent amination is feasible. When the parent compound **1** is subjected to the amination conditions, the dehydrodimer **11** (15%) is formed. When this pure material (**11**) is resubjected to the amination conditions, followed by acetylation, compound **26** is present in the mixture.

In conclusion, the reaction of 3-bromoimidazo[1,2-*a*]-pyridine (**2**) with strong nucleophiles leads to debromination, coupling, and various telesubstitution and Chichibabin amination products. No single mechanism can account for the formation of all of these. Displacement of bromine by direct substitution or by a benzyne-type mechanism does not occur, at least in the potassium amide reaction. It appears to be generally true that π-excessive heteroaromatic halides do not form benzyne-type intermediates. A number of precedents for telesubstitution spanning *one* six-membered ring are known.[25] More recently, after completion of this work, telesubstitution spanning both rings in polyazanaphthalenes has been described.[26] In all of the compounds undergoing teleamination, the halogen is relatively inert and the negative charge of the attacking amide ion can be placed on a ring nitrogen in the intermediate. In the case of compound **2** the amine group in the intermediate (**21**) must migrate before the observed product **13** can be formed, and this seems to be a novel combination of known reactions.

Further studies, to examine the validity of this telesubstitution mechanism, are in progress.

Experimental Section

Unless otherwise stated, Woelm neutral alumina, Brockmann grade 3, was used for chromatography and solutions were dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H NMR spectra were obtained with either a Varian HA-100 or a Hitachi Perkin-Elmer R-20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M, IR spectra with a Beckman Acculab 1 instrument. Elemental analyses[27] were determined by the Analytical Services Laboratory of The University of Alabama Chemistry Department or by Atlantic Microlab, Inc., Atlanta, Ga.

Imidazo[1,2-*a*]pyridine (1). While a number of synthetic routes are available,[28] the following simplified procedure leads to high yields (up to 100%). Prolonged heating of the acetal with acid must be avoided, and in order to achieve efficient salting out with NaCl, the product mixture must be acidified (to liberate CO_2) prior to basification. After a mixture of ethyl 2-bromoacetal (10 g, 0.05 mol), H_2O (40 mL), and concentrated HCl (1 mL, 0.012 mol) was stirrred vigorously for 2.5 h it was heated in an 80 °C oil bath for 0.5 h to give a clear solution. The cooled solution was treated with portions of $NaHCO_3$ (5.5 g, 0.065 mol) and 2-aminopyridine (3.8 g, 0.04 mol). The mixture was stirred overnight, acidified with concentrated HCl, treated with aqueous 10% NaOH to pH 9–10, saturated with NaCl, and extracted with $CHCl_3$ (4 × 20 mL). The extracts were dried over anhydrous Na_2CO_3, stripped of solvent, and distilled through a Vigreux column to give colorless compound **1** (bp 97–102 °C (0.25 Torr) (lit.[1b] bp 112–117 °C (3 Torr)) which turned dark overnight.

3-Bromoimidazo[1,2-*a*]pyridine (2), prepared by the NBS procedure[1b] (76%), was crystallized from hexane. Chromatography (C_6H_6) of the materials in the mother liquor also gave pure compound **2,** mp 90.5–91.5 °C (lit.[1b] mp 92.9–93.4 °C, lit.[9] mp 92–94 °C), which can be sublimed (90 °C (0.05 Torr)). The NaOBr procedure[9] gave lower yields (45–55%).

Reaction of Compound 2 with Methyllithium. A solution of compound **2** (3.0 g, 0.015 mol) in anhydrous Et_2O (100 mL) in a dry three-neck flask, equipped with stirrer, condenser (protected with Drierite), and septum, was stirred and cooled in ice. When ethereal CH_3Li (1.9 M, 12.0 mL) was added with a syringe during 3 min, an immediate white solid separated. The mixture was stirred for 45 min and then treated dropwise with H_2O (30 mL). The H_2O layer was saturated with NaCl and extracted with $CHCl_3$ (4 × 10 mL). The combined Et_2O and $CHCl_3$ layers were dried and stripped of solvents to give a mixture (ca. 1:1) of compounds **1** and **3** (^1H NMR). To an ice-cold swirled solution of the mixture (0.37 g) in concentrated H_2SO_4 (1.5 mL) was added dropwise concentrated HNO_3 (0.5 mL). After 5 min, the solution was poured onto ice and treated with aqueous 20% NaOH until no further solid separated. The yellow solid had the same melting point (mp 202–203 °C (lit.[9] mp 203–204 °C)) and IR spectrum as an authentic sample of **3-nitroimidazo[1,2-*a*]pyridine (4).**

The mixture of compounds **1** and **3** was subjected to chromatography (C_6H_6); the process was repeated on fractions enriched in compound **3.** The material in the fraction showing greatest enrichment in compound **3** (^1H NMR) was treated with picric acid in absolute EtOH. The picrate, after three recrystallizations from large volumes of absolute EtOH, had mp 231–232.5 °C, undepressed on admixture with picrate of authentic compound **3.**

3-Methylimidazo[1,2-*a*]pyridine Picrate (3·picrate). A hot ethanolic solution (1 mL) of compound **3**[1b] (0.13 g, 1 mmol) was treated with picric acid (0.23 g, 1 mmol) in hot EtOH (2 mL). The picrate (92%) after three crystallizations from absolute EtOH (100 mL) had mp 231–233 °C.

Reaction of Compound 2 with Lithium Ethylamide. A dry three-neck flask, equipped with stirrer, a dry ice/acetone condenser filled with ice and NaCl and protected with Drierite, and a gas inlet tube, was flushed with N_2 and charged with anhydrous Et_2O (50 mL) which was then cooled in an ice–NaCl bath (−13 °C). $EtNH_2$ was passed into the Et_2O until the volume had increased by ca. 10 mL. The gas inlet tube was replaced by a septum through which ethereal MeLi (96 mL, 1.9 M) was injected with a syringe while the mixture was stirred and cooled (colorless solid separated). A solution of compound **2** (3.75 g, 19 mmol) in anhydrous Et_2O (75 mL) was added during 20 min (black solids separated) and stirring was continued for 40 min. Volatile materials were removed at room temperature in a stream of N_2, Et_2O (40 mL) was added, and the process was repeated. Et_2O (50 mL) was added, the mixture was cooled in ice, Ac_2O (25 mL) was added dropwise during 10 min, and the mixture was warmed to drive off the Et_2O and then heated on a steam bath overnight. The mixture was treated with H_2O (25 mL), heated 10 min, and stripped of solvents under reduced pressure. The residue was treated with H_2O, ice, and aqueous 20% NaOH to pH 8 to give a black solid from which the aqueous solution was decanted. $CHCl_3$ extraction (6 × 30 mL) of the solution gave a mixture containing large amounts of Ac_2NEt and AcNHEt (^1H NMR), which were removed by treating the mixture with 1 N HCl to pH 2 and continuously extracting with $CHCl_3$. The $CHCl_3$ extracts contained no aromatic materials (^1H NMR). The acidic solution was treated with aqueous 20% NaOH (ice) and extracted with $CHCl_3$ (5 × 25 mL). The black solid A was extracted with boiling $CHCl_3$ (2 × 25 mL) and these extracts were combined, dried, and subjected to chromatography ($CHCl_3$) which gave the parent compound **1** (0.8 g, 35%) and compound **5** contaminated with **1** (0.17 g). Fractional sublimation gave compound **5,** mass spectrum mol wt 239 and 241, which was converted into its picrate for analysis. After three recrystallizations from absolute EtOH, compound **5**·picrate had mp 209–210 °C dec.

Reaction of Compound 2 with Lithium Diethylamide. Dry Et_2NH in a three-neck flask equipped with a condenser (protected with Drierite) and stirrer was cooled in ice, stirred, and treated with a hexane solution of *n*-BuLi (15 mL, 2.4 M) followed by the addition during 10 min of a solution of compound **2** (2.96 g, 0.015 mol) in anhydrous Et_2O (75 mL). After 1 h the dark mixture was treated with HCl (15 mL, 2.4 M), heated on a steam bath, and stripped of solvents under reduced pressure. The $CHCl_3$ soluble portion of the residue was separated by chromatography ($CHCl_3$) into fractions I (compounds **7** and **2**), II (compounds **9, 1, 10,** and **8**), and III (compounds **8** and **10**). Fraction I was subjected to molecular distillation (80 °C (0.05 Torr)) followed by chromatography (C_6H_6) to give the liquid compound **7** which was converted into its picrate for analysis. After four recrystallizations from absolute EtOH, it had mp 117.5–118.5 °C.

Fraction II was further separated by chromatography (20% CH_3CN/C_6H_6) into fractions IV (compounds **9, 1,** and **10**), V (compounds **1** and **8**), and VI (compound **8**). Fraction VI was subjected to molecular distillation (110 °C (0.05 Torr)) and then became a waxy solid. Fraction V was fractionated by chromatography (5% CH_3CN/C_6H_6) into compounds **1** and **8.** The latter was converted into its picrate which after two recrystallizations from 90% EtOH had mp 217–218 °C.

Fraction IV was separated by chromatography (2.5% CH_3CN/C_6H_6) into mixtures and pure compounds **9** and **10.** Compound **9,** mass spectrum mol wt 189, was converted into its picrate, which after crystallization from EtOH had mp 176–177 °C. Compound **10,** mass spectrum mol wt 260, failed to give a crystalline picrate derivative.

The percent yields shown in Table II, derived from ^1H NMR

spectra and weight of the various fractions, are estimated to be within 10% of their actual values.

When the lithium diethylamide reaction was carried out at a lower temperature (−35 °C), TLC indicated that an equally complex mixture was formed.

Reaction of 3-Bromoimidazo[1,2-a]pyridine (2) with Potassium Amide. A. To liquid NH_3 (250 mL), stirred in a three-neck flask, equipped with a dry ice/acetone condenser protected with solid KOH pellets in a drying tube, was added K metal (ca. 0.2 g) and a small crystal of ferric nitrate hydrate. Further 0.50 g portions of K (total of 3.5 g, 0.09 mol) were added whenever the blue color faded. A solution of compound **2** (3.5 g, 0.018 mol) in anhydrous Et_2O (100 mL) was added dropwise during 30 min. The dark mixture was stirred for an additional 2 h. NH_4Cl (4.6 g, 0.087 mol) was added and the mixture was stirred overnight to evaporate NH_3. The Et_2O was evaporated on a steam bath in a stream of N_2. The residue was heated with Ac_2O (40 mL) for 2.5 h on a steam bath, cooled, treated with H_2O (40 mL), heated on the steam bath for 10 min, and stripped of solvents under reduced pressure. After the residue was dissolved in H_2O (50 mL), cooled in ice, and treated with aqueous 20% NaOH to pH 9, the precipitated black and colorless solids (A) (3.13 g) were filtered and rinsed with H_2O. The filtrate was saturated with NaCl and continuously extracted with $CHCl_3$ for 2 days to give a brown oil (1.0 g) which on sublimation (room temperature, 0.05 Torr) yielded acetamide (0.55 g). The residue (0.43 g) consisted of starting material (**2**), acetamide, and compound **14** (mass spectrum and TLC).

Extraction of the solids (A) with boiling $CHCl_3$ (6 × 35 mL) left an insoluble black powder (0.83 g), mp >310 °C, which could not be purified, showed amide absorption in the IR, and is believed to be polymeric. The residue of the $CHCl_3$ extracts was dissolved in EtOH, concentrated (15 mL), treated with H_2O (25 mL), cooled, and scratched to give a solid that was recrystallized (charcoal) from EtOH/H_2O to give compound **14** (1.49 g) as fine colorless needles, mp 167.5–168 °C. The residue from the mother liquor gave a black $CHCl_3$-insoluble material (0.18 g). Chromatography on Silica of the $CHCl_3$-soluble portion gave diacetamide and compound **14** (0.05 g, 50% total) as the only identifiable solids.

B. A similar amination mixture was stirred for 5 h and worked up as above to give compound **14** as major product. Noncrystallizable, $CHCl_3$-soluble materials, on chromatography ($CHCl_3$), gave trace amounts that contained a substance with the same R_f as compound **19.** Elution with 2% absolute EtOH/$CHCl_3$ gave a mixture which, after treatment with charcoal in EtOH, crystallized from aqueous 30% EtOH as dense kernels (35 mg) and a powdery solid (90 mg) which were sorted by hand. The dense kernels, compound **26,** crystallized by dissolving in EtOH/H_2O and evaporating the EtOH, had mp 289 °C, amide absorption in the IR, and mass spectrum mol wt 291 (later scans showed a contaminant, presumably a diacetamidodehydrodimer, with *m/e* ca. 348). Compound **26** had the same R_f (alumina, 2% MeOH/$CHCl_3$) as compound **14** but gave a brown color with I_2 whereas the latter gives a purple color. The powdery solid, on preparative TLC (silica gel, 15% MeOH/$CHCl_3$), contained three major components (11 lines), compounds **14** and **26,** and a compound with mass spectrum mol wt 175, mp 222 °C (softens 193 °C), whose IR spectrum showed amide absorption but differred from the spectra of the isomeric compounds **14** and **17–20.** No evidence was obtained for the presence of either compound **20** or **18.**

C. A similar reaction mixture (3.5 g K, no ferric nitrate, and 3.5 g of compound **2**) was stirred for 2.75 h prior to the NH_4Cl addition. The solvents were evaporated and the oily residue was extracted with $CHCl_3$. The insoluble portion was further extracted with $CHCl_3$ (Soxhlet) to give a semisolid (2.37 g total). Chromatography (2% absolute EtOH/C_6H_6) afforded compounds **1** (0.3 g, 10%) and **11** (0.25 g, 8%). Elution with 10% absolute EtOH/C_6H_6 gave a fraction of predominantly one material (0.35 g) which was treated with Ac_2O (1 mL) on a steam bath for 1 h, heated 10 min with H_2O (1 mL), and stripped of solvents. Addition of ice/water to the black residue, followed by aqueous 10% NaOH, gave compound **26** (0.27 g, 7%), mp >300 °C, which was purified by dissolution in MeOH, charcoal treatment, and boiling down to the beginning of crystal formation. Three crystallizations afforded an analytical sample.

Formation of 5,5′-Biimidazo[1,2-a]pyridyl (11) from Imidazo[1,2-a]pyridine (1). To KNH_2 (1.8 g K, 45 mmol; a crystal of ferric nitrate hydrate) in liquid NH_3 (100 mL) was added dropwise with stirring a solution of compound **1** (2.0 g, 17 mmol) in anhydrous Et_2O (30 mL) during 0.5 h. After 5 h, NH_4Cl (2.5 g, 49 mmol) was added and the solvents were evaporated. The residue was heated on a steam bath for 2.5 h with Ac_2O (25 mL) and was then treated with H_2O (25 mL) and stripped of solvents. The residue was treated with H_2O (20 mL) and aqueous 10% NaOH to pH 9–10. The solution was decanted from a dark gum and both were extracted with $CHCl_3$. The $CHCl_3$-insoluble portion of the gum (0.87 g) could not be purified. The $CHCl_3$ extracts were stripped of solvent and the residue was extracted with C_6H_6. Chromatography ($CHCl_3/C_6H_6$ mixtures) of the extract gave compounds **1** (0.20 g) and **11** (0.22 g, 12%). Compound **11** was triturated with C_6H_6, dissolved in EtOH, and treated with charcoal. Water (2.5 mL) was added and the solution was boiled down to crystal formation. After another EtOH/H_2O treatment followed by sublimation (150 °C (0.25 Torr)), compound **11** had mp 247.5–249 °C, mass spectrum mol wt 234. The C_6H_6 insoluble portion on chromatography ($CHCl_3$) gave compound **11** (0.05 g, 15% total) and a small amount of material, mp >310 °C, mass spectrum mol wt 466, and IR spectrum similar to that of compound **11.**

Reaction of the Dehydrodimer (11) with Potassium Amide. A mixture of KNH_2 (0.32 g K, 8 mmol), liquid NH_3 (30 mL), Et_2O (10 mL), and compound **11** (0.12 g, 0.5 mmol) was stirred for 4 h. The reaction was quenched with NH_4Cl (0.47 g, 8.8 mmol) and solvents were evaporated to give an orange residue that was extracted with hot $CHCl_3$ (5 × 8 mL). TLC (alumina, 10% absolute EtOH/$CHCl_3$) indicated the presence of much starting material and three other components, R_f 0.55, 0.75, and 0.85. The major components of the chromatogram fraction from which the acetamidodehydrodimer (**26**) had been obtained in the reaction of KNH_2 with compound **2** (see part C, above) had R_f 0.55. Evaporation of $CHCl_3$ gave a residue (0.11 g) which was treated with Ac_2O (0.5 mL) on a steam bath for 1 h. Addition of H_2O (1 mL) and evaporation under reduced pressure gave a thick oil that was treated with H_2O (5 mL) and aqueous 10% NaOH to pH 10, followed by extraction with $CHCl_3$ (3 × 5 mL). TLC (alumina, $CHCl_3$) indicated the presence of compound **11** and three components, R_f 0.10, 0.25, and 0.40. The acetamidodehydrodimer (**26**) obtained from compound **2** had R_f 0.25.

3,3′-Dinitro-5,5′-biimidazo[1,2-a]pyridyl (25). Compound **11** was dissolved in ice-cold concentrated H_2SO_4 (0.80 mL) and concentrated HNO_3 (0.3 mL) was added dropwise with stirring. The pale yellow solution was left to stand at room temperature for 30 min and then poured onto ice (10 g) and partially neutralized with aqueous 20% NaOH (pH ca. 2). The yellow solid was filtered, rinsed with H_2O, and dried at 60 °C (0.25 Torr) to give compound **25** (0.12 g, 96%): mp darkens >150 °C and explodes at 205 °C with formation of a purple solid; calcd mol wt 324; mass spectrum mol wt 279 (324 + H − NO_2). An analytical sample was obtained as fine yellow needles from 1,2-dimethoxyethane.

3,3′-Dinitro-7-acetamido-5,5′-biimidazo[1,2-a]pyridyl (27). After compound **26,** (70 mg, 0.24 mmol) was dissolved in chilled concentrated H_2SO_4 (0.7 mL), concentrated HNO_3 (0.3 mL) was added dropwise with stirring. The solution was left to stand at room temperature for 40 min and ice and aqueous 20% NaOH were added until precipitation was complete (pH 1–2). Filtration and rinsing with H_2O gave a yellow powder (90 mg, 98%), mp 85 °C dec. On attempted crystallization from EtOH, the material partially decomposed.

3-Nitro-8-acetamidoimidazo[1,2-a]pyridine (32), prepared as above from compound **18,** was recrystallized three times from absolute EtOH to give an analytical sample as fine yellow needles, mp 222.5–223.5 °C (no dec, changes to kernels >210 °C).

3-Nitro-5-methylimidazo[1,2-a]pyridine (31). To a chilled solution of 5-methylimidazo[1,2-*a*]pyridine[29] (0.50 g, 3.8 mmol) in concentrated H_2SO_4 (4.0 mL) was added dropwise concentrated HNO_3 (1.0 mL) with stirring. The solution was stirred for 25 min at room temperature, poured onto ice, and partially neutralized with solid NaOH, to give a brown powder (0.20 g), which was dissolved in 1,2-dimethoxyethane (15 mL), treated with charcoal, filtered, and concentrated (2 mL) to yield sturdy yellow needles, mp 115–116 °C, soluble in most solvents, including H_2O from which it can be crystallized. An analytical sample, twice crystallized from hexane, and then sublimed rapidly (100 °C/0.25 Torr), was obtained as fine yellow needles,[30] mp 115.9–117.2 °C.

2,5-Diaminopyridine. A mixture of 5-nitro-2-aminopyridine[31] (2.8 g, 20 mmol), EtOH (25 mL), and 10% Pd/C was hydrogenated in a Paar shaker (initial pressure 49 psi) for 2 days, filtered through Celite, concentrated to dryness under reduced pressure, and dried (room temperature, 0.25 Torr) to give 2,5-diaminopyridine as a purple solid, mp 95–98 °C (lit.[32] mp 108–110 °C).

6-Acetamidoimidazo[1,2-a]pyridine (14). A mixture of H_2O (20 mL), concentrated HCl (1.0 mL) and ethyl 2-bromoacetal (5.5 g, 28 mmol) was refluxed for 1.5 h, cooled, and treated with $NaHCO_3$ (5.5 g, 65 mmol) followed by all of the 2,5-diaminopyridine (prepared above) dissolved in H_2O (15 mL). At once a dark solid separated and CO_2 was evolved. After the mixture was refluxed for 20 h, then cooled, a black solid was filtered and discarded. The filtrate was saturated with NaCl and extracted with $CHCl_3$ (5×). After drying, the extract

was stripped of solvent to give a light brown solid (1.1 g, 41%) which rapidly turned green and could be sublimed (140 °C (0.25 Torr)) to give colorless needles that turned green on exposure to air and had mp ~110–117 °C dec. To all of the material was added Ac_2O (5 mL). Before all had dissolved, another colorless material separated. The mixture was briefly heated on a steam bath to effect solution and was then chilled over ice. The precipitate was filtered, rinsed with Ac_2O and acetone, and identified to be the acetic acid salt of compound **14** (1.27 g, 65%) by its IR spectrum. The solid was dissolved in H_2O (5 mL) and treated with aqueous 10% NaOH to pH 10. The precipitated nearly colorless compound **14** was purified by dissolution in EtOH (10 mL), treatment with charcoal, addition of H_2O (6 mL), and boiling down (8 mL). Sublimation (160–180 °C (0.25 Torr)) afforded an analytical sample, mp 168–170 °C dec.

5-Acetamidoimidazo[1,2-*a*]pyridine (17). 5-Aminoimidazo[1,2-*a*]pyridine, was sublimed (150 °C (0.1 Torr)) to give off-white crystals. On standing it turned dark and was black after several weeks. Freshly sublimed compound (0.29 g) was heated with Ac_2O (1.25 mL) on a steam bath for 0.5 h then treated with H_2O (1.5 mL), heated for 5 min, and stripped of solvents under reduced pressure. Addition of H_2O (1 mL) and aqueous 10% NaOH to pH 9–10 gave a solid (0.35 g, 92%) which was dissolved in EtOH (10 mL), treated with charcoal, and filtered. Addition of H_2O (5 mL) and concentrating the solution (5 mL) gave long colorless needles, which were sublimed (140 °C (0.1 Torr)) to give an analytical sample, mp 146.5–147 °C.

8-Acetamidoimidazo[1,2-*a*]pyridine (18) was prepared by Paudler and Blewitt's[1b] general method of refluxing a solution of ethyl 2-bromoacetal (5.5 g, 28 mmol) in pure dioxane (15 mL), H_2O (4 mL), and concentrated HCl (0.4 mL) for 0.5 h, cooling, adding $NaHCO_3$ (5.5 g, 65 mmol), followed by 2,3-diaminopyridine (2.2 g, 20 mmol), refluxing for 12 h, cooling, making basic with aqueous 10% NaOH (pH 10), and extracting with $CHCl_3$ (4 × 25 mL). The extract was decanted from a dark oil, dried, filtered through Celite, and stripped of solvent to give a viscous dark oil (2.7 g). An Ac_2O solution (10 mL) of the crude product was refluxed for 45 min, cooled, treated with H_2O (10 mL), boiled for 10 min, stripped of solvents, and treated with H_2O and aqueous 10% NaOH (to pH 9) to give nearly colorless compound **18** (2.6 g, 74%). It was purified by dissolution in EtOH (30 mL), treatment with charcoal, addition of H_2O (20 mL), and boiling down (25 mL). Sublimation gave an analytical sample as sturdy crystals, mp 144–145 °C.

2-Acetamidoimidazo[1,2-*a*]pyridine (19), prepared according to Bristow[21] and recrystallized from absolute EtOH, had mp 228–229 °C (lit.[21] mp 229 °C).

3-Acetamidoimidazo[1,2-*a*]pyridine (20), mp 196–197 °C (lit.[9] mp 197 °C), was prepared according to Paolini and Robins,[9] except that 3-nitroimidazo[1,2-*a*]pyridine was reduced to 3-aminoimidazo[1,2-*a*]pyridine in the presence of Pd/C in lieu of Raney Ni.

2-Methylimidazo[1,2-*a*]pyridine was prepared according to Paudler and Blewitt.[1]

6-Bromoimidazo[1,2-*a*]pyridine, 33, prepared in 65% yield by the general method[1] of refluxing an aqueous EtOH solution of 5-bromo-2-aminopyridine[33] with bromoacetaldehyde, was purified by chromatography (50% $C_6H_6/CHCl_3$). Sublimation (80 °C (0.05 Torr)) gave an anlytical sample, mp 78.5–80 °C (lit.[28b] mp 53–55 °C).

Registry No.—**3** picrate, 66358-17-6; **5** picrate, 66358-18-7; **7** picrate, 66358-19-8; **8** picrate, 66358-20-1; **9** picrate, 66358-21-2; **26,** 66358-22-3; ethyl 2-bromoacetal, 2032-35-1; 2-aminopyridine, 504-29-0; lithium ethylamide, 50835-31-9; lithium diethylamide, 816-43-3; 2,5-diaminopyridine, 4318-76-7; 5-nitro-2-aminopyridine, 4214-76-0; 5-aminoimidazo[1,2-*a*]pyridine, 66358-23-4; 2,3-diaminopyridine, 452-58-4; 5-bromo-2-aminopyridine, 1072-97-5.

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(12) Unpublished results.
(13) The major aspects of this work were presented at the ACS Meeting in Miniature, Tuscaloosa, Ala., 1974.
(14) A slight preponderance of compound **3** was present in the mixture obtained with CH_3Li.
(15) This type of reaction is frequently employed in the preparation of organolithium compounds. See, for example, "Organic Reactions", Vol. VI, R. Adams, Ed., Wiley, New York, N.Y., 1951, p 339.
(16) Coupling is frequently observed especially with long reaction times, during halogen–lithium exchange reactions. See ref 15 and W. Langham, R. Q. Brewster, and H. Gilman, *J. Am. Chem. Soc.*, **63,** 545 (1941).
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(34) Of a number of other mechanisms we had considered, the one (also suggested by a reviewer) involving attack by a second $^-NH_2$ on **21** was rejected in view of the formation of the 8-NEt_2 compound (**7**). If a self-consistent mechanism is to obtain for these $^-NR_2$ reactions, the σ complex initially formed by addition to C-7 then yields **23** in which attack by another bulky NEt_2 moiety at C-8 is severely hindered by the C-7 NEt_2 group and the peri lone pair of electrons on N-1. Such constrairts are absent in the postulated intramolecular aziridine formation.

Potassium–Graphite as a Metalation Reagent. Synthesis of Aldehydes and Ketones by Alkylation of Imines and Dihydro-1,3-oxazine

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The metalating properties of potassium–graphite (C_8K) toward imines **1** and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (**4**) are described. Alkylation of the potassium salts **2** and **5** with a variety of alkyl halides affords in good yields the corresponding carbonyl compounds **3** and **6**. The Wurtz coupling of alkyl halides is a side reaction in tetrahydrofuran; it can be suppressed using hexane as solvent, but in this case the yield of alkylated imine is lower. The alkylation reaction is regioselective. The formation of the enaminic anion **2** in this reaction is confirmed by filtering under argon the solution from the solid reagent before adding the alkyl halide. By the same procedure it is possible to perform the condensation between *N*-2-propylidenecyclohexylamine (**1d**) and nonanal to give, after acidic hydrolysis, the corresponding β-hydroxy and α,β-unsaturated carbonyl compounds **13** and **14**.

In recent years reactions under heterogeneous conditions have found interesting applications in the synthesis of organic molecules, since several advantages can be accomplished.[1] The facile separation of the insoluble reagents from products is one of the most convenient features of the solid phase synthesis. This method reduces possible losses of substances and simplifies the choice of the solvent. For example, polymer bound reagents have been prepared and utilized by several research groups.[2]

Recently graphite has found application for trapping reagents between the carbon layers, thus affording new compounds which possess definite stoichiometry and show modified reactivity with respect to the bulk reagent.[3] In fact a large number of inorganic substances such as mineral acids, metals, metal halides, and oxides can penetrate between the carbon layers.[3] Intercalation occurs spontaneously or by electrolysis. Mineral acids such as H_2SO_4, H_3PO_4, and HNO_3 can be intercalated after chemical or anodic oxidation of the graphite.

The catalytic properties of graphite–bisulfate $C_{24}^{+}HSO_4^{-}\cdot 2H_2SO_4$ in the esterification of carboxylic acids with alcohols[4] and of graphite–$AlCl_3$ in the Friedel–Crafts alkylation with alkyl halides[5] have been investigated.

The oxidizing capacity of graphite–CrO_3 toward primary alcohols has been reported.[6] More recently graphite–NbF_5 was found to be an effective catalyst for the reduction of 2-chloropropane and its reactions with alkanes.[7]

Alkali metals such as K, Rb, and Cs can be easily intercalated in graphite.[8] Depending on the amount of potassium used, compounds of different stoichiometry can be obtained, i.e., C_8K, $C_{24}K$, $C_{36}K$, and $C_{48}K$, to which correspond structures with one, two, three, or more carbon layers between each potassium layer.[8] When potassium is inserted, the distance between the carbon layers is increased from 3.35 to 5.40 Å.[8] Potassium–graphite (C_8K), a bronze-colored powder obtained by melting potassium over graphite under argon, has been found to act as a catalyst in polymerization reactions[9] and in the nuclear and side-chain alkylation of aromatic hydrocarbons with ethylene.[10] Furthermore it has found application as a reducing agent toward carbonyl compounds[6] and metal carbonyls.[11]

Recently we have extended the application of potassium–graphite for the reductive cleavage of the carbon–sulfur bond in α,β- and β,γ-unsaturated sulfones to give alkenes in good yields.[12] We also found that C_8K exhibits metalating properties toward weakly acidic substrates;[13] indeed, aliphatic nitriles and esters afforded the corresponding alkylated products after treatment with C_8K and alkyl halides at low temperature.[13]

The promising results obtained prompted us to extend the study of the metalating properties of C_8K,[14] examining other substrates such as the imines of aliphatic carbonyl compounds and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine, in order to realize, by a sequence of reactions shown in Schemes I and II, a convenient method for the preparation of carbonyl compounds.

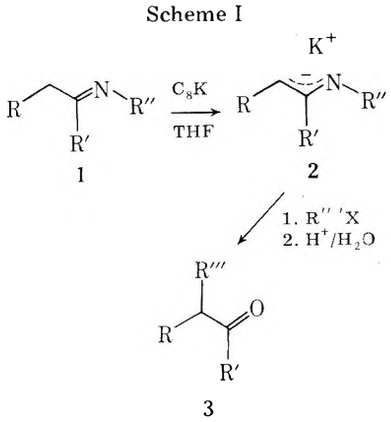
It is known that aliphatic imines, bearing a bulky *N*-alkyl group, are metalated at the α position by means of lithium dialkylamides,[15] or from lithium and dialkylamines in benzene–hexamethylphosphoric triamide.[16] The resulting metalated imines are known to be excellent nucleophiles.[15]

We have now found that imines **1** are easily metalated with a heterogeneous suspension of C_8K in tetrahydrofuran at room temperature to give the ion pairs **2** which are alkylated with alkyl halides affording, after hydrolysis, the corresponding carbonyl compounds **3** (Scheme I).

Similarly aldehydes **6** are obtained when 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (**4**) is used as starting material, following a reaction sequence which includes metalation with C_8K in THF at room temperature, alkylation with alkyl halides, reduction with sodium borohydride in aqueous ethanol, and hydrolysis with aqueous oxalic acid[17] (Scheme II).

As shown in Table I our procedure is very efficient for the formation of aldehydes and ketones. The data in Table I in-

Scheme I



R = H, alkyl, aryl; R′ = H, alkyl; R″ = *tert*-butyl, cyclohexyl; R‴ = alkyl; X = Cl, Br, I

Scheme II

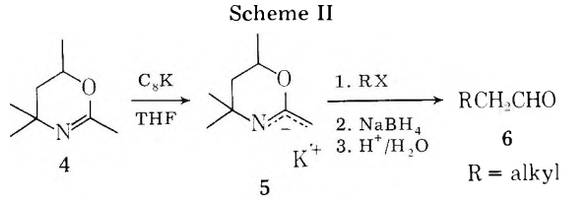


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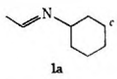
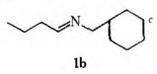
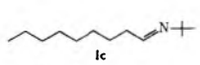
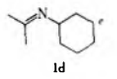
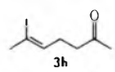
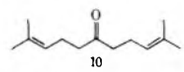
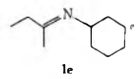
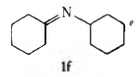
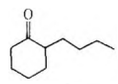
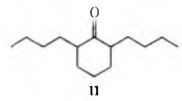
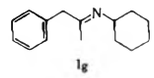
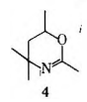
Table I. Carbonyl Compounds from Imines and 2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine[a]

Entry	Starting material	Registry no.	Alkyl halide	Registry no.	Carbonyl compd	Registry no.	Yield, %[b]
1	 1a	1193-93-7	1-$C_{13}H_{27}Br$	765-09-3	$C_{13}H_{27}CH_2CHO$ (**3a**) $(C_{13}H_{27})_2CHCHO$ (**7**)	2765-11-9 65899-12-9	64, 35[d] 8, 3[d]
2	**1a**		2-$C_8H_{17}Br$	557-35-7	$C_6H_{13}(CH_3)CHCH_2CHO$ (**3b**)	65899-13-0	63
3	 1b	1197-52-0	1-$C_7H_{15}Br$	629-04-9	$C_7H_{15}(C_2H_5)CHCHO$ (**3c**)	37596-40-0	70
4	**1b**		$C_6H_5CH_2CH_2$-Br	103-63-9	$C_6H_5CH_2CH_2(C_2H_5)CHCHO$ (**3d**)	33856-83-6	55
5	 1c	65956-94-7	1-C_4H_9Br	109-65-9	$C_7H_{15}(C_4H_9)CHCHO$ (**3e**)	65899-14-1	67
6	 1d	6407-36-9	1-$C_7H_{15}Br$		$C_8H_{17}COCH_3$ (**3f**) $(C_8H_{17})_2CO$ (**8**)	693-54-9 540-08-9	40, 35,[f] 48,[g] 25[h] 20, 5,[f] 40,[g] 8[h]
7	**1d**		$C_6H_5CH_2Cl$	100-44-7	$C_6H_5CH_2CH_2COCH_3$ (**3g**) $(C_6H_5CH_2CH_2)_2CO$ (**9**)	2550-26-7 5396-91-8	55 8
8	**1d**			870-63-3	 3h	110-93-0	64
					 10	2520-57-2	9
9	 1e	6125-75-3	1-$C_8H_{17}Br$	111-83-1	$C_9H_{19}COCH_2CH_3$ (**3i**)	1534-27-6	66
10	 1f	10468-40-3	1-C_4H_9Br		 3j	1126-18-7	56
					 11	65899-15-2	8
11	 1g	65899-11-8	1-C_4H_9Br		$C_6H_5(C_4H_9)CHCOCH_3$ (**3k**) $C_6H_5(C_4H_9)CHCOC_5H_{11}$ (**12**)	54929-04-3 65899-16-3	70 9
12	 4	26939-18-4	1-C_3H_7I	107-08-4	C_4H_9CHO (**6a**)	110-62-3	50
13			$C_6H_5CH_2Cl$		$C_6H_5CH_2CH_2CHO$ (**6b**)	104-53-0	58

[a] The general procedure is reported in the Experimental section. In all cases reported the molar ratio imine/C_8K/alkyl halide is 1:2:2. [b] Yields refer to pure isolated carbonyl compounds and are calculated on starting imines or oxazine. Analytical GLC yields of alkylated imines are always about 10% higher with respect to those of carbonyl compounds reported in the table. [c] See ref 15d. [d] The metalated imine is filtered under argon from the excess of C_8K and then allowed to react with 1 equiv of the alkyl halide. [e] See ref 20. [f] Molar ratio imine/C_8K/alkyl halide = 1:1:1. [g] Molar ratio imine/C_8K/alkyl halide = 1:4:4. [h] The reaction is performed at room temperature in hexane, instead of THF, with molar ratio imine/C_8K/alkyl halide (1:2:1). [i] See ref 17.

dicate that the optimum conditions for monoalkylation of imines are obtained with a molar ratio substrate/C_8K/alkyl halide 1:2:2 (entry 6).

The Wurtz coupling reaction of the alkyl halide in tetrahydrofuran with C_8K always accompanies the alkylation reaction, especially if C_8K is used in large excess; therefore a corresponding amount of alkyl halide is required. With hexane as solvent instead of THF, the Wurtz product disappears, thus no excess of alkyl halide is necessary. However, the yield of alkylated product is, in this case, lower (entry 6).

The reaction seems to have a wide applicability, giving good results with primary, secondary, allylic, and benzylic halides. In the same way both ketimines and aldimines can be employed in this reaction. As amine components of the Schiff's bases, cyclohexylamine and *tert*-butylamine were found to be suitable, since Schiff's bases having branched *N*-alkyl groups have less tendency toward self-addition than those with unbranched chains.

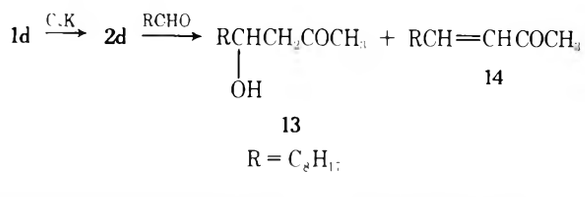
The alkylation reaction is regioselective.[18] In fact *N*-2-butylidenecyclohexylamine (**1e**) and *N*-1-phenyl-2-propylidenecyclohexylamine (**1g**) reacted with alkyl halides to give alkylated products at the methyl or methylene group, respectively[18] (entries 9 and 11).

Little of the α,α'-dialkylated ketimines were observed, while in the case of aldimines only *N*-ethylidenecyclohexylamine (**1a**) gave a partially dialkylated product.

Metalated imines **2** may be regarded as ambident anions. In fact partial alkylation at the nitrogen atom (about 5%) was observed treating the potassium salt of *N*-cyclohexylidenecyclohexylamine (**2f**) with bromobutane[19] (entry 10).

To ascertain that alkylation of imines occurs through the anion intermediate **2** as shown in Scheme I, experiments were performed where imines were treated with C_8K as previously described, then the solution was filtered by means of a bench-top apparatus under argon and allowed to react with an electrophile. Thus using *N*-ethylidenecyclohexylamine (**1a**) and 1-bromotridecane, pentadecanal (35%) was obtained. With the same procedure as described above, the reaction of

Scheme III



N-2-propylidenecyclohexylamine (**1d**) with nonanal as the electrophile afforded 4-hydroxydodecan-2-one (**13**) (30%) and dodeca-3-en-2-one **14** (5%) (Scheme III).

Finally, we wish to emphasize that the good yield obtained in this alkylation reaction, the inexpensiveness of the reagent, and the simplicity of workup may provide an attractive synthetic alternative to previously reported methods involving bases such as lithium alkylamides[15] or poisonous solvents such as hexamethylphosphoric triamide.[16]

Experimental Section

General. Infrared spectra (IR) were recorded on a Perkin-Elmer 710B spectrometer and are given in reciprocal centimeters. Nuclear magnetic resonance spectra (NMR) were determined in tetrachloromethane on a Perkin-Elmer R12B spectrometer. Chemical shifts are expressed as δ in ppm from internal tetramethylsilane. Mass spectra (MS) were taken on a Varian MAT 111 (70 eV). Vapor-phase chromatography was performed on a Hewlett Packard 5750 B instrument using 0.25 in. × 6 ft columns of 2% FFAP (nitroterephtalic acid) and 5% SF96 (silicon oil) on 80/100 mesh silanized Chromosorb G. TLC were performed on silica gel HF_{254} (Merck) and column chromatography on silica gel (Merck, 0.05–0.20 mesh) with hexane–ether as solvent. Tetrahydrofuran (THF) was obtained anhydrous and oxygen free by distillation over sodium benzophenone ketyl under argon. Graphite was supplied from Roth (impurities less than 500 ppm) and potassium from Carlo Erba (RPE, 99.5%). Melting points (mp) and boiling points (bp) are uncorrected.

General Procedure. Preparation of Aldimines and Ketimines. To a solution of cyclohexylamine (0.11 mol) in 30 mL of ether, 20 g of anhydrous sodium sulfate and the aldehyde or ketone (0.10 mol) were added at −20 °C with stirring. The mixture was allowed to stand at room temperature for 10 h, sodium sulfate was filtered off, the solvent was evaporated, and the residue was distilled under vacuum. Aldimines and ketimines **1** obtained in about 90 and 70% yield, respectively, were identified by the characteristic IR and NMR frequency values:[21] IR ν 1665–1670 cm^{-1} (C=N); NMR δ 7.6–7.8 (CH=N), 2.2 (CH_2C=N), 1.8–1.9 ppm (CH_3C=N).

Among the prepared imines **1** two were not reported in the literature. ***N*-Nonylidene-*tert*-butylamine (1c)** had bp 85 °C (0.1 mm): IR (neat) 1650 (C=N); NMR δ 7.65 (CH=N, t, 1 H), 2.2 (CH_2CH=N, m, 2 H), 1.1 (t-C_4H_9, s, 9 H); MS *m/e* 197 (M^+). ***N*-2-(1-Phenylpropylidene)cyclohexylamine (1g)** had bp 155–160 °C (15 mm): IR (neat) 1660 (C=N); NMR δ 7.3 (C_6H_5, s, 5 H), 3.5 ($C_6H_5CH_2C$=N, s, 2 H), 1.75 (CH_3C=N, s, 3 H); MS *m/e* 215 (M^+).

Preparation of Potassium–Graphite (C_8K). In a two-necked flask flushed with argon and equipped with a magnetic stirrer, 3.84 g (0.32 mg-atom) of graphite was stirred and heated with a bunsen flame under argon in order to desorb any oxygen and water. Then 1.6 g of potassium (0.04 mg-atom) was added in small pieces to the stirred graphite previously heated to about 200 °C. C_8K, a bronze-colored powder, was so obtained. It is easily prepared but must be handled in inert atmosphere since it is water sensitive and pyrophoric.

Alkylation and Hydrolysis of Imines. Synthesis of Aldehydes and Ketones. A solution of the imine (20 mmol) in 30 mL of THF was added over 10 min at room temperature to a heterogeneous mixture of C_8K (40 mmol) in 20 mL of THF. After 1 h a solution of the alkyl halide (40 mmol) in 20 mL of THF was dropped over 30 min. Stirring was continued for 2 h, then the excess of C_8K was quenched with 2 mL of water; the graphite was filtered and washed with ether. Solvent was evaporated and the residue was vigorously stirred with 100 mL of 4% oxalic acid aqueous solution at 0 °C for 3 h. After extraction with ether, the organic phase was evaporated and the residue was chromatographed on a silica gel column. The Wurtz coupling hydrocarbon was eluted with hexane, then the carbonyl compound was collected eluting with hexane/ether (98:2).

Pentadecanal (3a): mp 24 °C (hexane); IR (neat) 1720 (C=O); NMR 9.9 (t, 1 H, CHO), 2.3 (m, 2 H, CH_2CHO); MS *m/e* 226 (M^+).

2-Tridecylpentadecanal (7): mp 48–50 °C (hexane); IR (Nujol) 1720 (C=O); NMR 9.7 (d, 1 H, CHO), 2.3 (m, 1 H, CHCHO).

3-Methylnonanal (3b): bp 104 °C (18 mm); IR (neat) 1725 (C=O); NMR 9.9 (t, 1 H, CHO), 2.3 (dd, 2 H, CH_2CHO); MS *m/e* 156 (M^+).

2-Ethylnonanal (3c): bp 108 °C (18 mm); IR (neat) 1715 (C=O); NMR 9.45 (d, 1 H, CHO), 2.5 (m, 1 H, CHCHO); MS *m/e* 170 (M^+).

2-Ethyl-4-phenylbutanol (3d): bp 148 °C (22 mm); IR (neat) 1720 (C=O); NMR 9.7 (d, 1 H, CHO), 7.2 (s, 5 H, C_6H_5), 2.6 (t, 2 H, $C_6H_5CH_2$); MS *m/e* 176 (M^+).

2-Butylnonanal (3e): bp 115 °C (16 mm); IR (neat) 1715 (C=O); NMR 9.45 (d, 1 H, CHO), 2.35 (m, 1 H, CHCHO); MS *m/e* 198 (M^+).

Decan-2-one (3f): bp 96 °C (12 mm); IR (neat) 1715 (C=O); NMR 2.35 (t, 2 H, CH_2CO), 2.05 (s, 3 H, CH_3CO); MS *m/e* 156 (M^+).

Heptadecan-9-one (8): mp 53 (hexane); IR (Nujol) 1705 (C=O); NMR 2.3 (t, 4 H, CH_2COCH_2).

4-Phenylbutan-2-one (3g): bp 115 °C (13 mm); IR (neat) 1715 (C=O); NMR 7.2 (s, 5 H, C_6H_5), 2.7 (m, 4 H, CH_2CH_2), 1.95 (s, 3 H, CH_3CO); MS *m/e* 148 (M^+).

1,5-Diphenylpentan-3-one (9): bp 230 °C (18 mm); IR (neat) 1710 (C=O); NMR 7.2 (s, 10 H, $2C_6H_5$), 2.7 (m, 8 H, $2CH_2CH_2$); MS *m/e* 238 (M^+).

6-Methylhept-5-en-2-one (3h): bp 173 °C; IR (neat) 1710 (C=O); NMR 5.15 (m, 1 H, CH=C), 2.35 (t, 2 H, CH_2CO), 2.1 (m, 2 H, CH_2C=C), 2.0 (s, 3 H, CH_3CO), 1.7 and 1.6 (s, 6 H, $2CH_3C$=C); MS *m/e* 126 (M^+).

2,10-Dimethylhendeca-2,9-dien-6-one (10): bp 117 °C (15 mm); IR (neat) 1720 (C=O); NMR 5.15 (m, 2 H, CH=C), 2.3 (t, 4 H, $2CH_2CO$), 2.05 (m, 4 H, $2CH_2C$=C), 1.7 and 1.6 (s, 12 H, $4CH_3C$=C); MS *m/e* 194 (M^+).

Dodecan-3-one (3i): bp 134 °C (18 mm); IR (neat) 1710 (C=O); NMR 2.3 (m, 4 H, $2CH_2CO$); MS *m/e* 184 (M^+).

2-Butylcyclohexanone (3j): bp 70 °C (2 mm); IR (neat) 1715 (C=O); NMR 2.2 (m, 3 H, CH_2CO and CHCO); MS *m/e* 154 (M^+).

2,6-Dibutylcyclohexanone (11): bp 168 °C (18 mm); IR (neat) 1710 (C=O); NMR 2.3 (m, 2 H, 2CHCO); MS *m/e* 210 (M^+).

3-Phenylheptan-2-one (3k): bp 95 °C (2 mm); IR (neat) 1705 (C=O); NMR 7.3 (s, 5 H, C_6H_5), 3.5 (t, 1 H, CHCO), 2.0 (s, 3 H, CH_3CO); MS *m/e* 190 (M^+).

5-Phenylhendecan-6-one (12): bp 167–170 °C (18 mm); IR (neat) 1710 (C=O); NMR 7.2 (s, 5 H, C_6H_5), 3.5 (t, 1 H, CHCHO), 2.3 (t, 2 H, CH_2CO); MS *m/e* 246 (M^+).

Alkylation of 2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine. Synthesis of Aldehydes. The oxazine **4** (20 mmol) was metalated with C_8K (40 mmol) in dry THF and alkylated with alkyl halide (40 mmol) by a procedure identical to that reported for the imines. The crude alkylated oxazine was directly reduced to tetrahydrooxazine by means of $NaBH_4$ (20 mmol) in THF–EtOH (1:1) and successively hydrolyzed to aldehyde by 4% oxalic acid aqueous solution, as described by Meyers.[17]

Pentanal (6a): bp 103 °C; IR (neat) 1720 (C=O); NMR 9.8 (t, 1 H, CHO), 2.4 (dt, 2 H, CH_2CHO); MS *m/e* 86 (M^+).

3-Phenylpropanal (6b): bp 104 °C (13 mm); IR (neat) 1720 (C=O); NMR 9.7 (t, 1 H, CHO), 7.2 (s, 5 H, C_6H_5), 2.5 (m, 4 H, CH_2CH_2); MS *m/e* 134 (M^+).

Reaction of *N*-2-Propylidenecyclohexylamine (1d) with Nonanal. C_8K (40 mmol) was prepared in a two-necked flask connected by a fritted tube to a second flask equipped with an argon inlet. A solution of *N*-2-propylidenecyclohexylamine (**1d**) (2.8 g, 20 mmol) in dry THF (20 mL) was added to the suspension of C_8K in THF (40 mL) at room temperature under stirring. After 2 h the apparatus was overturned and a clear green solution of **2d** was vacuum filtered through the frit under argon and collected into the second flask. Nonanal (2.84 g, 20 mmol) in THF (20 mL) was added at −60 °C and the reaction was stirred for 1 h and then allowed to reach room temperature and quenched with water (10 mL).

After usual workup, the residue was chromatographed on silica gel to afford 1.11 g (30%) of 4-hydroxydodecan-2-one (**13**) and 0.17 g (5%) of dodeca-3-en-2-one (**14**).

4-Hydroxydodecan-2-one (13): bp 136 °C (12 mm); IR (neat) 3380 (OH), 1710 (C=O); NMR 4.0 (m, 1 H, CHOH), 2.8 (broad, 1 H, OH), 2.55 (d, 2 H, CH_2CO), 2.1 (s, 3 H, CH_3CO); MS of acetylated title compound, *m/e* 242 (M^+).

Dodeca-3-en-2-one (14): bp 97 °C (15 mm); IR (neat) 1670 (C=O); NMR 5.9–7.3 (m, 2 H, CH=CH), 2.1 (s, 3 H, CH_3CO); MS *m/e* 182 (M^+).

Acknowledgment. The authors are grateful to Dr. G. Passeri for his valuable help.

Registry No.—**2d**, 65899-17-4; **13**, 65899-18-5; **14**, 66142-11-8; C_8K, 12081-88-8; cyclohexylamine, 108-91-8; nonanal, 124-19-6; 1-phenylpropan-2-one, 103-79-7.

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Conformational Studies of Some 2-*exo*-Alkyl-3-benzyl-3-azabicyclo[3.3.1]nonanes

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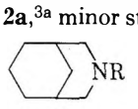
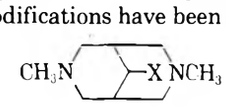
The conformations of three 3-benzyl-3-azabicyclo[3.3.1]nonanes substituted with 2-exo-alkyl groups have been studied by analysis of their proton and carbon-13 nuclear magnetic resonance spectra. These compounds were prepared by stereoselective alkylation of aldimmonium ion **4** with Grignard reagents. The presence of 2-methyl and 2-ethyl substituents was shown to cause the ring system to prefer a flattened double-chair conformation similar to that of the unsubstituted compound (**3a**). Introduction of a 2-isopropyl substituent, however, caused a change in favor of the chair–boat conformation.

Considerable attention has been directed toward synthesis and conformational analysis of substituted bicyclo[3.3.1]-nonanes and heterocyclic analogues, compounds which have potential as models for extension of the concepts and theories of stereochemistry.[1] In this connection, our interest has been centered on the 3-azabicyclo[3.3.1]nonane ring system (**1**). According to relative energy minima, **1** may exist in any of four conformations: double chair, chair–boat, boat–chair, and double boat. The most stable conformer of **1** is the double chair, as is the case with its *N*-alkyl analogues.[2] However, in this and in the conformationally similar diazabicyclic compound **2a**,[3a] minor structural modifications have been shown



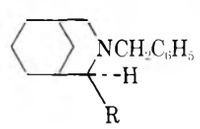
1



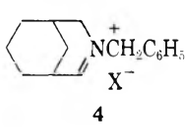
2a, X = H
b, X = OH

to cause conformational changes. For example, the methiodide of **1** (R = CH_3) and *N,N'*-dimethylbispidinol (**2b**) appear to prefer chair–boat conformations.[3b,c] While there have been a number of conformational studies of symmetrical derivatives of **1** and isomers, less information is available concerning the conformational preferences of unsymmetrical derivatives. Accordingly, we have investigated the effect of 2-*exo*-alkyl substituents on the conformation of **1**.

Among other methods, proton magnetic resonance (^{1}H NMR) spectrometry has proven to be effective in resolving configurational and conformational features in azabicyclic systems.[4] More recently, carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrometry has been shown to be a particularly powerful tool in such studies.[5] In this paper, we report the synthesis of 3-benzyl-3-azabicyclo[3.3.1]nonane (**3a**) and three of its 2-*exo*-alkyl analogues (**3b–d**) and some conclusions regarding the preferred conformations of these last compounds as determined from analysis of their ^{1}H and ^{13}C NMR spectral features.



3a, R = H
b, R = CH_3
c, R = CH_2CH_3
d, R = *i*-C_3H_7



4

Results and Discussion

Compounds **3b–d** were each prepared from **3a** in two steps.[6] Oxidation of **3a** with bromine in methylene chloride[7] furnished aldimmonium salt **4** (X = bromide or perchlorate).

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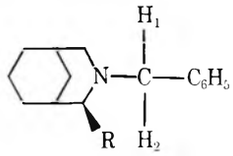
Table I. ^{1}H NMR Spectral Features of 2-Alkyl-3-benzyl-3-azabicyclo[3.3.1]nonanes[a]

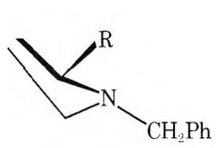


Compd	Registry no.	Chemical shifts, ppm (J, Hz)[a]		
		CCH_3 of R	Aliphatic NCH_2 and NCH	H_1; H_2
3a	19015-40-8		1.95–2.29 (dd,[b] 2 H), 2.65–3.00 (dd,[b] 2 H)	3.28 (s); 3.28 (s)
3b	66224-91-7	0.97 (d) (7)	2.52–3.17 (m, 3 H)	3.42 (d); 3.62 (d) (14)
3c	66224-92-8	0.75 (t) (7)	2.50–2.90 (m, 3 H)	3.45 (d); 3.65 (d) (14)
3d	66224-93-9	0.88 (d) (7), 1.00 (d) (7)	2.15–2.45 (m, 2 H), 2.90–3.20 (m, 1 H)	3.50 (d); 4.07 (d) (14)

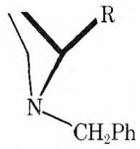
[a] Spectra were taken at 60 MHz using chloroform-*d* as solvent and 1% tetramethylsilane as an internal standard. Aromatic protons were seen as broad singlets centered at 7.31 ppm (average value). [b] J_1 = 10.5 Hz and J_2 is unresolved.

Addition of this salt to an excess of the appropriate Grignard reagent gave **3b–d**. The relative configurational assignment of the alkyl groups in these compounds is based on the assumption that nucleophilic attack will be from the less hindered exo side of **4**, in analogy with the reported preference for addition of various nucleophiles to bicyclo[3.3.1]non-2-ene and bicyclo[4.3.1]dec-2-ene derivatives.[8]

^{1}H NMR Studies. The extent of chemical shift nonequivalence in benzylic methylene protons in ^{1}H NMR spectra[9] has been utilized not only in determination of relative configurations of piperidines,[10a] piperazines,[10] and 1-azadecalins[11] but also in qualitative conformational analysis of heterocyclic and azabicyclic systems.[3,12] From these investigations it has become clear that nonequivalence will be observed in these cyclic systems if the benzyl group is vicinal to a single equatorial alkyl substituent, as in **5**.[10c,12] However, if this substituent is axial as in **6**, nonequivalence will not be seen.[10c]



5



6

Salient features in the ^{1}H NMR spectra of **3a–d** are shown in Table I. The benzylic methylene protons of **3b–d** exhibit observable nonequivalence. The chemical shift difference between these protons is 0.20 ppm in **3b** and **3c** and is increased to 0.57 ppm in **3d**. Based on the above analysis, two explanations may be offered to account for this increase. The isopropyl group could cause an increased disparity in benzyl rotamer populations in **3d** relative to **3b** and **3c**,[13] assuming that all three compounds prefer the conformation in which their alkyl groups are equatorial, as represented by partial structure **5**. This in turn would result from a more severe steric interaction of the isopropyl substituent with the benzyl group in **3d**, as compared with that of the methyl and ethyl substituents with this group in **3b** and **3c**, respectively. In support of this, inspection of molecular models of these compounds showed that the methyl and ethyl substituents should have about the same influence on benzyl group rotamer populations, with the isopropyl substituent having an increased influence. Alternatively, the greater $\Delta\delta$ could be due to a predominance, in **3d**, of conformer **5** over conformer **6**, with a relatively smaller percentage of **5** (greater percentage of **6**) representing both **3a** and **3b**.

Consideration of the region of the spectra in which aliphatic *N*-methylene and *N*-methine protons are found lends further support to the contention that **5** best represents the heterocyclic ring in **3d** but casts doubt as to the conformations of this ring in **3b** and **3c**. The spectrum of **3d** features a broad one proton multiplet centered at 3.05 ppm and a two proton multiplet at 2.15–2.45 ppm. From analysis of the ^{1}H NMR spectra of numerous related cyclic and polycyclic compounds, it has been suggested that protons anti to the nitrogen lone pair electrons appear below 2.50 ppm and those gauche to these electrons between 2.70 and 3.10 ppm.[14] Therefore, **3d** has two protons anti and one proton gauche to the lone pair, indicative of the predominance of conformer **5**. The spectra of **3b** and **3c** exhibit no signals indicative of anti protons, but multiplets integrating for three protons are present in the region of the spectra where gauche protons are generally found. These data do not seem to support the presence of either **5** or **6** as being representative of the heterocyclic ring of **3b** and **3c**.

In order to clarify the conformational preferences of the ring systems in **3a–d** in general and in **3b** and **3c** in particular, a comparison of their ^{13}C NMR spectra was made.

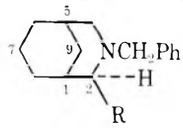
^{13}C NMR Studies. The sensitivity of carbon-13 chemical shifts to changes in molecular geometry is the basis for the application of ^{13}C NMR spectrometry in conformational analysis.[5,15]

In Table II are listed the carbon-13 chemical shifts of compounds **3a–d**. Assignments were made in the following manner. Off resonance decoupled spectra were obtained in order to distinguish between methyl, methylene, and methine carbon atoms. Most of the individual assignments of methylene and methine carbons of **3b–d** could be made by consideration of the ^{13}C NMR shift values of **3a** and related bicyclo[3.3.1]nonanes,[16] taking into account the anticipated substituent parameters.

In addition to the greater complexity of the spectra of **3b–d** in relation to that of **3a**, consistent differentiating features are the positions of C-4, C-9, and the benzylic methylene carbons, which are found at 6.1–7.5, 5.3–6.2, and 4.6–5.8 ppm upfield from the corresponding carbons in the spectrum of **3a**, respectively. The upfield shift of the benzylic methylene carbons is indicative of steric congestion due to the presence of the 2-alkyl groups; those of C-4 and C-9 seem to be due to stereochemical features which will be discussed below.

The spectral positions of C-7 and C-2′ appear to provide the most unambiguous evidence regarding the ring system conformations of **3b–d**. A 5.0 ppm upfield shift of C-7 is seen in **3d** relative to **3a**. Based on the ^{1}H NMR spectral characteristics of **3d** (see above), which suggested that its piperidine ring was mainly in the boat conformation, we attribute this difference to a gauche relationship of the 7-*endo*-hydrogen with the endo hydrogens at C-2 and C-4. This interaction has been proposed to account for the ca. 5 ppm upfield shift of C-7 in the spectra of chair–boat conformers with respect to those of

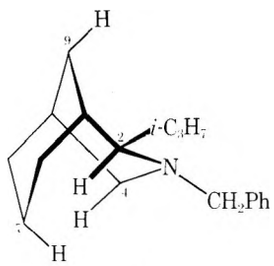
Table II. ^{13}C Chemical Shifts of 2-Alkyl-3-benzyl-3-azabicyclo[3.3.1]nonanes[a]



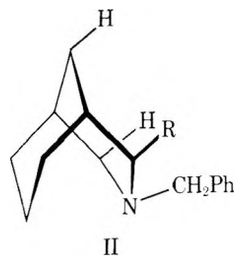
Compd	R	C-1	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-2′	CH_2Ph[e]
3a	H[b]	29.7	59.9	(59.9)	(29.7)	31.5	22.6	(31.5)	34.4		64.3
3b	CH_3	35.5	57.7	52.4	29.6	32.8[c]	22.1	32.0[c]	28.3	10.1	59.7
3c	C_2H_5	29.9[c]	65.1	52.9	29.3[c]	32.7[d]	22.0	32.0[d]	28.2	15.4[f]	59.5
3d	i-C_3H_7	27.7[c]	67.2	53.8	29.1[c]	33.0[d]	17.6	31.6[d]	29.1	27.2[c,f]	58.5

[a] Spectra were taken using chloroform-*d* as solvent. Shifts are given in ppm downfield from internal tetramethylsilane. [b] Chemical shifts of symmetry-related atoms are enclosed in parentheses. [c,d] These assignments are interchangeable. [e] Phenyl ring carbons were found at 140.3 (α-C), 128.7 (σ-C), 128.0 (m-C), and 126.4 (p-C) ppm (average values). [f] Chemical shifts for C–CH_3: **3c**, 11.8 ppm; **3d**, 16.2 and 19.8 ppm.

chair–chair conformers in the closely related 9-azabicyclo[3.3.1]nonan-3-ols.[16b] This implies that the cyclohexane ring of **3d** prefers the chair conformation and that the overall ring system may be best represented by I. Since the



I



II

position of C-7 in **3b** and **3c** does not differ greatly from that in **3a**, the gauche endo hydrogen relationship must not be present, and the rings of all of these compounds therefore appear to prefer a flattened double-chair conformation (II; R = H, CH_3, and C_2H_5).

Additional evidence in favor of these conformational representations is provided by the position of C-2′: methyl, methylene, and methine in the spectra of **3b–d**, respectively. The methyl carbon of **3b** is seen at 10.1 ppm, which is about 10 ppm upfield from its position in 2-methylpiperidine derivatives in which it assumes an equatorial orientation.[17] We attribute this high-field position to a gauche relationship of it with the 4-*exo*- and 9-*syn*-hydrogens, as a result of its being in an axial orientation (conformer II; R = CH_3). When one of the hydrogens of this group is replaced with a methyl group, the resulting methylene is shifted downfield by 5.3 ppm. Since the substituent parameter for α-CH_3 in piperidines is 5.4 ppm,[17b] the downfield shift of this methylene seems to be due primarily to the influence of the methyl group and not to any reduction in its proximity with respect to the 4-exo- and 9-*syn*-hydrogens. Replacement of another hydrogen with a methyl group, giving **3d**, would be expected to result in a further shift of C-2′ to about 20.6 ppm. However, C-2′ is found at least 6.6 ppm farther downfield, presumably as a result of the relief of steric crowding due to a shift in favor of conformer I.

The positions of C-2, C-4, and C-9 in the spectra may be interpreted in a manner consistent with the above analysis. In **3b** and **3c** the C-4 carbon is shifted 7.5 and 7.0 ppm upfield relative to its position in **3a** due to the gauche interaction of the 2-*exo*-alkyl groups with the respective 4-*exo*-hydrogens.[17b] This effect is partially offset at C-2 in **3b** by the downfield shift caused by the α-CH_3 contribution, resulting in a net upfield shift of only 2.2 ppm relative to C-2 in **3a**; in **3c** the effect at C-2 is overridden by downfield α-CH_2 and β-CH_3 contributions, resulting in a net downfield shift of 5.2 ppm. In **3d**, C-4 is shifted 6.1 ppm upfield relative to its position in **3a** due to the gauche 2,4,7-*endo*-hydrogen interaction. This relationship also undoubtably causes C-2 to appear upfield from where it would appear in the absence of such an interaction, but the magnitude of the relative difference cannot be reliably estimated due to the lack of a suitable reference compound.

The upfield shift of C-9 in **3b** and **3c** relative to its position in **3a** is due to the *syn*-9-hydrogen–2-*exo*-alkyl interaction, and in **3d** relative to **3a** is probably due to transannular shielding by the nitrogen lone pair electrons on the 9-*syn*-hydrogen.[18]

Conclusion

The ^1H and ^{13}C NMR spectral features of **3d** indicate that it prefers a chair–boat conformation (I). Analysis of the ^{13}C NMR spectra of **3b** and **3c** shows them to prefer flattened double-chair conformations, similar to that of **3a**, while the observable nonequivalence of the benzylic methylene protons in the ^1H NMR spectra of these compounds implies the presence of the chair–boat conformer. However, in these compounds this nonequivalence, suggestive of close proximity of the 2-alkyl and 3-benzyl substituents, seems to result from conformational flattening rather than from the presence of equatorial alkyl groups.

Experimental Section

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) and 60-MHz proton magnetic resonance spectra were obtained using Beckman IR 33 and Hitachi R 20A spectrometers. Carbon-13 magnetic resonance spectra were measured at 25.035 MHz with a Joel JNM PS-100 spectrometer interfaced with a Jeol JEC-980A computer, using 10-mm tubes. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Analytic gas–liquid chromatography (GLC) was done using a Perkin-Elmer 881 gas chromatograph equipped with flame ionization detection: carrier gas, helium (30 mL/min); detector gasses, hydrogen (40 mL/min) and compressed air (250 mL/min); temperatures, injection port (210 °C), oven (150 °C), and detector (210 °C); 6 ft × 0.125 in stainless steel column containing 3% OV-17 on Gas Chrom Q (80–100 mesh), ca. 2400 theoretical plates (calcd). Reactions were monitored by thin-layer chromatographic analysis, which was carried out using 5 × 10 cm glass plates precoated with 0.25-mm layers of silica gel GF (Analtech): developing solvent, chloroform–methanol–28% aqueous ammonia (95:5:0.5) unless stated otherwise; spots were visualized with iodine vapor.

General Methods. All reactions were carried out under dry nitrogen. Solutions of products were concentrated on a Buchi Rotavapor (10–40 mm) at water bath temperatures of 40 °C or less. Free bases of hydrochloride salts were prepared by partitioning them between ether and 10% aqueous sodium hydroxide, followed by drying (anhydrous sodium sulfate) and concentration as above. Traces of water in the samples were removed azeotropically with benzene in vacuo.

3-Benzyl-3-azabicyclo[3.3.1]nonane (3a) was prepared as described previously.[19] Its hydrochloride salt was crystallized from chloroform–carbon tetrachloride, mp 215–216 °C subl (lit.[19] 217 °C subl).

3-Benzyl-3-azoniabicyclo[3.3.1]non-2-ene Bromide (4). To 200 mL of methylene chloride was added 7.52 g (35 mmol) of **3a** and 31.5 g (296 mmol) of anhydrous sodium carbonate. To the magnetically stirred mixture was added dropwise a solution of 6.76 g (42 mmol) of bromine in 100 mL of methylene chloride over a period of 1.5 h. After stirring for another 2 h, the mixture was filtered and concentrated to give a red solid, which separated from ethyl acetate–ether as white crystals: 3.5 g (34%); TLC showed one spot, R_f 0.5. A small amount of this was converted to the perchlorate salt and crystallized from ethanol: mp 126–127.5 °C; IR (KBr) 1680 cm^{-1} (C=N$^+$) (lit.[20] mp 122 °C, IR (KBr) 1669 cm^{-1}).

2-*exo*-Methyl-3-benzyl-3-azabicyclo[3.3.1]nonane (3b). To a cold (0 °C) 1 M solution of methylmagnesium bromide in tetrahydrofuran (5 mL) was added 0.185 g (0.5 mmol) of **4** bromide in one portion. The stirred suspension was allowed to warm to room temperature, and after 15 h excess Grignard reagent was destroyed by the addition of 30% aqueous ammonium chloride. The supernatant was decanted and the precipitate washed with tetrahydrofuran. The combined organic extracts were concentrated. The residue was dissolved in ether and dried (anhydrous sodium sulfate), and the solution was treated with excess ethereal hydrogen chloride. The precipitate was crystallized from chloroform–carbon tetrachloride: 0.06 g (35%); mp 197–202 °C (darkening).

Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.32; H, 9.12; N, 5.35.

This salt was converted to the free base: GLC retention time of 5.8 min and ca. 100% purity.

2-*exo*-Ethyl-3-benzyl-3-azabicyclo[3.3.1]nonane (3c). To 1.0 mL of 1.3 M ethereal ethylmagnesium bromide was added 0.056 g (0.18 mmol) of **4** perchlorate in one portion. After stirring for 24 h, the reaction mixture was found to contain no starting material by TLC analysis. Excess Grignard reagent was destroyed as above, the residual solvent decanted, and the precipitate washed well with ether. The combined extracts were dried (anhydrous sodium sulfate) and concentrated to give 0.02 g (46%) of a colorless oil: GLC retention time of 7.7 min and >99% purity. This was dissolved in ether and, excess ethereal hydrogen chloride was added. The precipitate was crystallized from chloroform–carbon tetrachloride, mp 204.5–207 °C (darkening).

Anal. Calcd for $C_{17}H_{26}ClN$: C, 72.96; H, 9.37; N, 5.01. Found: C, 72.85; H, 9.38; N, 5.05.

2-*exo*-Isopropyl-3-benzyl-3-azabicyclo[3.3.1]nonane (3d). The reaction of 0.58 g (2 mmol) of **4** bromide with 10 mL of 1 M ethereal isopropyl magnesium bromide was carried out in the same way as that used to prepare **3c**. After stirring for 4.5 h, TLC analysis indicated complete consumption of the starting material. Excess Grignard reagent was destroyed as before, 10-mL portions of ether and water were added, and the aqueous phase was adjusted to ca. pH 7 with 10% aqueous hydrochloric acid. The ether layer was removed, and the aqueous phase was reextracted with two 10-mL portions of ether. The combined ethereal extracts were dried (anhydrous sodium sulfate) and concentrated to give 0.34 g of a yellow oil. TLC analysis (the developing solvent was methylene chloride–methanol, 90:10) showed four components. The product was chromatographed on 26 g of 60–200 mesh silica gel. Elution with 100 mL of methylene chloride followed by 300 mL of 1% methanol in methylene chloride gave two fractions. TLC analysis of the first fraction (the developing solvent was methylene chloride–methanol, 99:1) indicated the presence of two components (R_f 0.32 and 0.63), the first of which (major) was indistinguishable from an authentic sample of **3a** and the second of which (minor) was not identified. Analysis of the second fraction revealed a single component (R_f 0.06). This fraction was concentrated, and the residue was dissolved in ether and treated with excess ethereal hydrogen chloride. The precipitate was crystallized from chloroform–carbon tetrachloride: 0.11 g (19%); mp 217–219 °C (darkening).

Anal. Calcd for $C_{18}H_{28}ClN$: C, 73.57; H, 9.60; N, 4.77. Found: C, 73.47; H, 9.60; N, 4.69.

The free base was prepared from 0.1 g of this salt: GLC retention time of 11.3 min and ca. 98% purity.

Acknowledgment. We are grateful to Professor J. R. Wiseman for recommending the ^{13}C NMR experiments and for his suggestions concerning the conformational properties of **3a–d**. Thanks are extended to Mr. Courtney Pape for recording the ^{13}C NMR spectra. This work was supported by an NIH Biomedical Research Grant administered by the University of Georgia.

Registry No.—**3a** HCl, 23481-98-3; **3b** HCl, 66224-94-0; **3c** HCl, 66224-95-1; **3d** HCl, 66224-96-2; **4** Br^-, 66224-97-3; **4** ClO_4^-, 66224-99-5.

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The Chemistry of Thionitroxyl Radicals

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Acetylenes react with bisamine disulfides to give thiophenes. The decomposition of bis(*N*-benzyl-*N*-methylamine) disulfide proceeds by dissociation to a thionitroxyl radical which abstracts a benzylic hydrogen atom to give the products *N*-benzylmethylamine, *N*-methylbenzalimine, and sulfur. Morpholinothionitroxyl radical also abstracts benzylic hydrogen atoms.

Thionitroxyl radicals are formed reversibly by most bisamine disulfides.[1,2] In some cases the disulfides decompose to sulfur, amine, and imine or to thioamides, which appear to be formed from amine and sulfur and imine and sulfur. For example, at 140 °C in an evacuated sealed tube bis(dibenzylamine) disulfide decomposes to *N*-benzylthiobenzamide and dibenzylammonium hydrogen sulfide.[3]

The purpose of this research was to investigate the mechanism of decomposition of benzylic amine disulfides and the chemistry of thionitroxyl radicals.

Results and Discussion

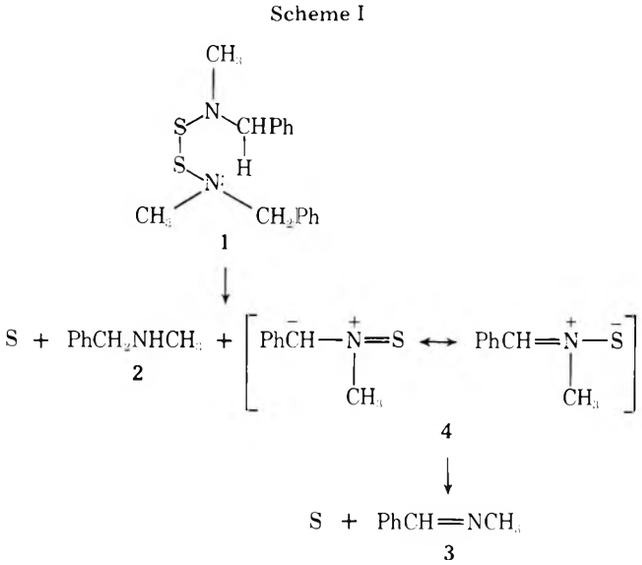
At 140 °C under nitrogen bis(*N*-benzyl-*N*-methylamine) disulfide (**1**) pyrolyzed to *N*-methylthiobenzamide. Upon attempted high vacuum distillation **1** decomposed to sulfur and a 1:1 molar ratio of *N*-benzyl-*N*-methylamine (**2**) and *N*-methylbenzalimine (**3**).

Inspection of space filling molecular models reveals that a benzylic hydrogen of one amino group lies in close proximity to the lone pair of electrons of the second amino group. Consistent with this geometry is a mechanism involving the fragmentation of **1** to a thionitrone **4** as shown in Scheme I.

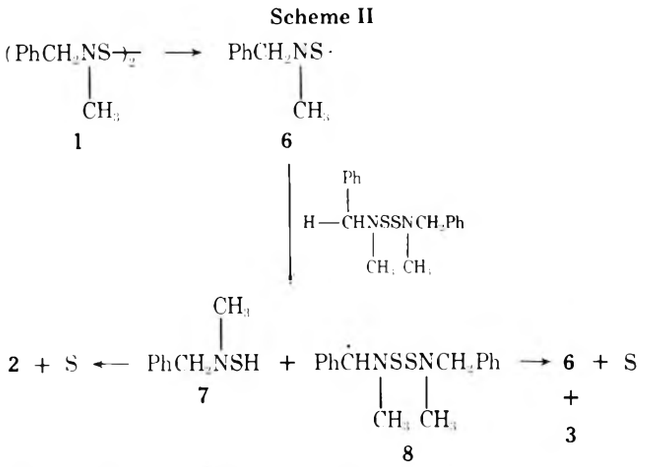
Since thionitrones might be expected to undergo 1,3 cycloaddition with acetylenes, the decomposition of the amine disulfide **1** was conducted in the presence of phenylacetylene. When run by adding acetylene to disulfide preheated to 110 °C, the reaction was violently exothermic and gave (*E*)-4,6-diphenyl-1,3-dithiafulvene (**5**) and a mixture of 2,4- and 2,5-diphenylthiophenes. The slow addition of disulfide to acetylene preheated to 140 °C was much less exothermic, and 2,4- and 2,5-diphenylthiophenes were formed in an 85:15 molar ratio and in 38% overall yield. No 1,3 cycloadduct was derived from the thionitrone **4**, and phenylacetylene was isolated by either procedure.

Bis(2,2,6,6-tetramethylpiperidine) disulfide, which lacks hydrogen atoms α to nitrogen and therefore cannot decompose to a thionitrone, also reacted with phenylacetylene to give an 82% yield of a mixture (85:15 molar ratio) of 2,4- and 2,5-diphenylthiophenes.[4]

Scheme I



Scheme II



The similarity of the diphenylthiophene isomer ratio for the reactions of **1** and the piperidine disulfide with phenylacetylene and the lack of a 1,3 cycloadduct from **4** and phenylacetylene rule out the thionitrone mechanism.

The mechanism we proposed earlier for diphenylthiophene formation upon reaction between tetramethylpiperidine disulfide and phenylacetylene involves initial dissociation of the disulfide to a thionitroxyl radical, which then adds to phenylacetylene to form an intermediate radical which collapses to a thiirene. The thiirene opens to a thioketocarbene, which undergoes cycloaddition with a second molecule of phenylacetylene to give thiophenes. The similarity of the diphenylthiophene isomer ratio for the reactions of **1** and the piperidine disulfide with phenylacetylene suggests that the decomposition of bis(*N*-benzyl-*N*-methylamine) disulfide (**1**) is initiated by dissociation of **1** to *N*-benzyl-*N*-methylthionitroxyl radical (**6**). Subsequently, **6** abstracts a benzylic hydrogen atom from a second molecule of **1** to form thiohydroxylamine **7** and benzylic radical **8**. Finally, **7** decomposes[5] to **2** and sulfur while **8** collapses to **3**, sulfur, and **6**, as shown in Scheme II.

In order to show that thionitroxyl radicals such as **6** are capable of benzylic hydrogen atom abstraction, bis(morpholine) disulfide (**9**) was separately reacted at 140 °C under nitrogen with *N*-benzyl-*N*,*N*-dimethylamine, **2**, and phenylacetonitrile.[6] Each reaction produced *N*-morpholinothiobenzamide (**10**), morpholine, and sulfur. The radical mechanism for these reactions is presented in Scheme III and is supported by the fact that molecular oxygen completely inhibits each reaction.

The formation of thiophenes upon reaction between bisamine disulfides and acetylenes appears to be fairly general.

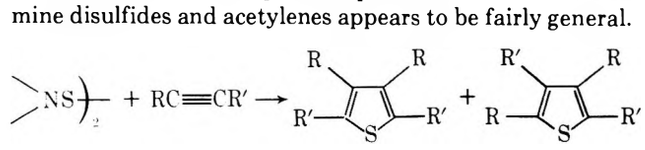


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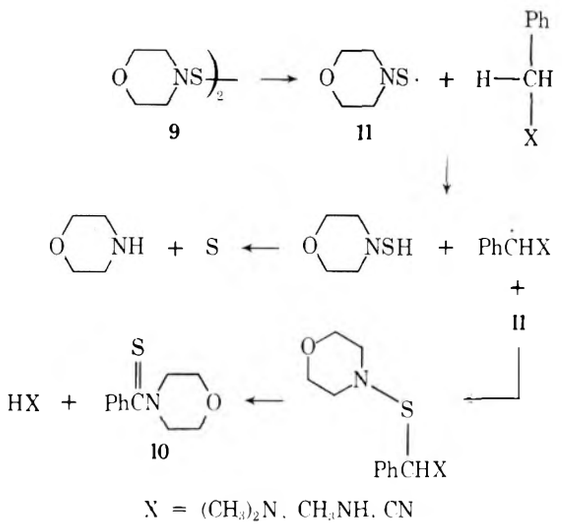
Table I

RC≡CR′ R	RC≡CR′ R′	Registry no.	Amine disulfide	Thiophene ratio 2,4	Thiophene ratio 2,5	Overall yield, %
H	Ph	536-74-3	1	85[f]	15[g]	38[a]
H	Ph		A[d]	85	15	82[a]
H	Ph		A	70	30	37[b]
H	Ph		B[d]	75	25	52[a]
H	Ph		B	85	15	37[b]
H	Ph		S_8[e]	100	0	38[b]
H	CO_2CH_3	922-67-8	B	0	100[h]	48[a]
H	CO_2CH_3		B	0	100	27[b]
Ph	$CO_2C_2H_5$	2216-94-6	B		100[c,i]	67[a]
CO_2CH_3	CO_2CH_3	762-42-5	B			38[a]
CO_2CH_3	CO_2CH_3		B			24[b]
Ph	Ph	501-65-5	A	0	0	No reaction[a]
H	$(CH_3)_3C$	917-92-0	A	0	0	S_8

[a] For 3 h at 140 °C. [b] For 24 h in refluxing chlorobenzene at 132 °C. [c] Diethyl 3,4-diphenyl-2,5-thiophenedicarboxylate. [d] A: bis(2,2,6,6-tetramethylpiperidine) disulfide; registry no., 14045-39-7. B: bis(morpholine) disulfide; registry no., 103-34-4. [e] Registry no.: S_8, 10544-50-0. [f] Registry no.: 3328-86-7. [g] Registry no.: 1445-78-9. [h] Registry no.: 4282-34-2. [i] Registry no.: 65818-64-6.

Scheme III

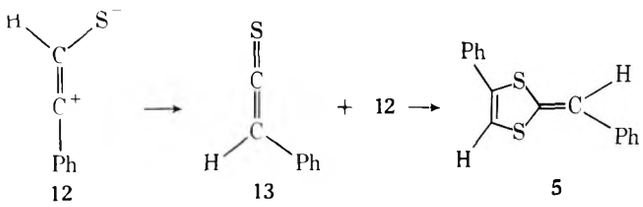


The preliminary results and the proposed thioketocarbene mechanism have been reported.[4] Here we present the experimental details and additional data as outlined in Table I. Yields are higher when the acetylene and disulfide are heated to 140 °C under nitrogen than when refluxed at 132 °C in chlorobenzene. The piperidine disulfide gives a higher overall yield of thiophene with phenylacetylene than morpholine disulfide with phenylacetylene.

Two symmetrical acetylenes give divergent results. Diphenylacetylene is unreactive, and dimethyl acetylenedicarboxylate gives tetramethyl thiophenetetracarboxylate in 38% yield. *tert*-Butylacetylene reacts with the piperidine disulfide to give sulfur but no thiophene. In this case, the intermediate thiirene or thioketocarbene decomposes to sulfur and *tert*-butylacetylene faster than it adds a second molecule of *tert*-butylacetylene to form a thiophene.

Thioketocarbenes are known to undergo 1,3-dipolar cycloaddition with carbon disulfide to form 1,3-dithiole-2-thiones.[7] The fact that we obtained 1,3-dithiole-2-thiones from reaction of carbon disulfide, acetylenes, and bisamine disulfides provides additional support for the proposed thioketocarbene mechanism. This reaction is reported in a subsequent paper.[8]

The formation of **5**, observed in the reaction between **1** and phenylacetylene discussed earlier, can now be understood as arising from the 1,3-dipolar cycloaddition between phenylthioketocarbene **12** and phenylthioketene **13**, which is produced by rearrangement[9] of **12**.



All of our results support the proposed thioketocarbene mechanism for thiophene formation from bisamine disulfides and acetylenes. However, we have conducted two experiments to eliminate the possibility that sulfur is responsible for the thiophene formation. First, morpholine and piperidine disulfides were recovered unchanged from refluxing chlorobenzene and from heating at 140 °C in a Parr bomb under nitrogen. Second, phenylacetylene reacted with sulfur in refluxing chlorobenzene to form 2,4-diphenylthiophene, exclusively.

In summary, the decomposition of **1** is initiated by dissociation to a thionitroxyl radical **6** which abstracts a benzylic hydrogen atom from **1** to form the thiohydroxylamine **7** and benzylic radical **8**, which then decompose to the observed products as shown in Scheme II.

Thionitroxyl radicals react with acetylenes to form thioketocarbenes which react with acetylenes, carbon disulfide, and phenylthioketene to form thiophenes, 1,3-dithiole-2-thiones and a dithiafulvene, respectively.

Experimental Section

All boiling points and melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 237 infrared spectrophotometer. NMR spectra were recorded on a Jeol-C-60M spectrometer with Me_4Si as an internal standard. Mass spectra were taken on an Hitachi Perkin-Elmer RMU-6 spectrometer with an ionizing potential of 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. The disulfide **9** was purchased from ICN Pharmaceuticals, Inc., and recrystallized from ethyl acetate before use. The amines **2** and *N*-benzyl-*N*,*N*-dimethylamine and the acetylenes phenylacetylene, ethyl phenylpropiolate, and dimethyl acetylenedicarboxylate were purchased from Aldrich Chemical Co., Inc., and methyl propiolate from Chemical Samples Co. The acetylenes diphenylacetylene[10] and *tert*-butylacetylene,[11] the disulfides[12,13] **1** and bis(2,2,6,6-tetramethylpiperidine) disulfide, and the imine[14] **3** were prepared according to the literature procedures.

Thermolysis of Bis(*N*-benzyl-*N*-methylamine) Disulfide (1). A distilling apparatus connected to a high vacuum line by all glass

fittings was charged with 15.2 g (0.05 mol) of **1** and heated to 140 °C at 1.0×10^{-4} mmHg. At this temperature 12.0 g of a colorless liquid was removed from an ice–water trap. The liquid was a mixture of imine **3** [1640 cm^{-1} (C=N)] and amine **2** [3280 cm^{-1} (N–H)]. Separation of **2** and **3** was accomplished by dissolving the liquid in Et_2O and extracting the resulting solution three times with 5% HCl. The ether layer was separated, dried ($MgSO_4$), and evaporated, giving 5.5 g (92%) of **3**: IR (neat) 3050, 2940, 2850, 1640, 1575, 1440, 1305, 1000, 900, 750, 690 cm^{-1}; mass spectrum, *m/e* (relative intensity) 119 (100), 118 (100), 103 (6), 102 (9), 91 (52), 78 (48), 77 (70), 63 (22), 51 (48), 42 (96).

The water layer was neutralized with Na_2CO_3 and extracted with Et_2O. The ether layer was separated, dried ($MgSO_4$), and evaporated, giving 6.0 g (99%) of **2**: IR (neat) 3280 cm^{-1}; mass spectrum, *m/e* (relative intensity) 121 (72), 120 (100), 119 (17), 118 (28), 92 (17), 91 (75), 78 (14), 77 (17), 44 (89), 42 (58).

The solid residue in the distilling flask was identified as sulfur in quantitative yield.

Heating 15.2 g of **1** under N_2 at atmospheric pressure at 140 °C for 1 h gave a residue from which 5.1 g of a mixture of **2** and **3** was distilled. Treatment of the pot residue with acetone gave a solid which was filtered and identified as sulfur. The acetone was evaporated to give a brown solid which was recrystallized from benzene–petroleum ether (30–60 °C) to give 2.5 g (33%) of *N*-methylthiobenzamide: mp 79 °C (lit.[15] mp 79 °C); IR (KBr) 3300, 1960, 1530, 1345, 1240, 1030, 945, 770, 690 cm^{-1}; mass spectrum, *m/e* relative intensity) 151 (88), 150 (59), 121 (100), 118 (36), 104 (15), 91 (24), 77 (94), 51 (70), 40 (76).

(*E*)-4,6-Diphenyl-1,3-dithiafulvene (5). To 15.0 g (0.05 mol) of **1** heated to 110–115 °C under N_2 was added 10.0 g (0.10 mol) of phenylacetylene dropwise. Upon completion of the addition the reaction became extremely exothermic, at which time the heat was removed. The cooled reaction mixture was treated with Et_2O, whereupon a yellow precipitate formed. Recrystallization of the solid in benzene gave 0.31 g (5%) of **5**: mp 197 °C (lit.[16] 197–198 °C; IR (KBr) 3055, 1550, 1482, 1430, 1183, 925, 895, 809, 735, 680 cm^{-1}; NMR (CCl_4) δ 6.30 (1, s), 6.37 (1, s), 7.14 (5, s), 7.25 (5, s); mass spectrum, *m/e* (relative intensity) 268 (100), 237 (12), 236 (18), 135 (11), 134 (90), 121 (45), 102 (29), 90 (49), 77 (28), 69 (20), 63 (31).

The ether was evaporated and the residue chromatographed over silica gel to give 8% of 2,4-diphenylthiophene and 32% of *N*-methylthiobenzamide.

General Procedure for Reactions between Phenylacetylene and Bisamine Disulfides. A molar ratio for phenylacetylene to bisamine disulfide was 4:1 for these experiments. To phenylacetylene maintained at 140 °C under N_2 was added bisamine disulfide over a 15-min period. The mixture was heated for 3 h, cooled, and evacuated on a high vacuum line (1×10^{-4} mmHg) for several hours to remove excess phenylacetylene. The residue was chromatographed on silica gel with petroleum ether (30–60 °C) as eluent, giving a mixture of 2,4- and 2,5-diphenylthiophenes. The thiophene mixture was separated using a GLC instrument fitted with a 6 ft SE-52 column and programmed from 100 to 300 °C at 30 °C/min with a flow rate of 30 mL/min. The retention times were 9.8 and 13.3 min for 2,4- and 2,5-diphenylthiophene, respectively. Experiments conducted by dissolving the same molar ratio of phenylacetylene to bisamine disulfide in 15 mL of chlorobenzene and refluxing for 24 h under N_2 were treated by the same procedure as above. The results are summarized in Table I.

General Procedure for Reactions between Bisamine Disulfides and Acetylenes. The acetylenes and either **9** or bis(2,2,6,6-tetramethylpiperidine) and disulfide were mixed together in a 4:1 molar ratio and heated for 3 h under N_2 at 140 °C. The reaction mixture was evacuated after cooling, and the resulting residue was chromatographed on silica gel. Experiments conducted in 15 mL of chlorobenzene were treated as mentioned in the preceding procedure.

Diethyl 3,4-Diphenyl-2,5-thiophenedicarboxylate. From 1.18 g (5.0 mmol) of **9** and 3.74 g (20.0 mmol) of ethyl phenylpropiolate, 1.27 g (67%) of the thiophene was formed: mp 141 °C (lit.[17] 141–142 °C); IR (KBr) 3075, 3000, 1730, 1700, 1450, 1375, 1310, 1230, 1100, 1010, 770, 700 cm^{-1}; NMR (CCl_4) δ 1.1 (6, H, J = 7.0 Hz), 4.1 (4, q J = 7.0 Hz), 7.0 (10, m); mass spectrum, *m/e* (relative intensity) 380 (100), 335 (41), 305 (48), 287 (62), 263 (14), 234 (31), 189 (41), 89 (28), 77 (7), 51 (10).

Dimethyl 2,5-Thiophenedicarboxylate. From 0.67 g (8.0 mmol) of methyl propiolate and 0.47 g (2.0 mmol) of **9**, 0.20 g (48%) of the thiophene was formed: mp 149 °C (lit.[18] 184–149 °C); IR (KBr) 2990, 2950, 1710, 1590, 1475, 1430, 1250, 800 cm^{-1}; NMR (CCl_4) δ 3.80 (6, s), 8.42 (2, s); mass spectrum, *m/e* (relative intensity) 200 (15), 171 (19), 169 (42), 156 (15), 140 (31), 114 (31), 112 (100), 82 (23), 43 (31).

Tetramethyl Thiophenetetracarboxylate. From 1.18 g (5.0 mmol) of **9** and 2.84 g (20.0 mmol) of dimethyl acetylenedicarboxylate, 0.61 g (39%) of the thiophene was formed: mp 125 °C (lit.[19] 125–126 °C); IR (KBr) 2999, 1710, 1540, 1460, 1250, 975 cm^{-1}; NMR (CCl_4) δ 3.90 (s); mass spectrum, *m/e* (relative intensity) 316 (29), 285 (100), 227 (10), 198 (10), 111 (36), 59 (77).

***N*-Morpholinothiobenzamide (10).** A solution of 5.4 g (40.0 mmol) of *N*-benzyl-*N*,*N*-dimethylamine and 1.18 g (5.0 mmol) of **9** was refluxed for 3 h under N_2. After cooling 10 mL of Et_2O was added, causing the precipitation of **10**. Recrystallization from Et_2O gave 0.9 g (87%): mp 137–138 °C (lit.[6] 137–138 °C). IR (KBr) 2950, 2900, 2840, 1485, 1468, 1420, 1325, 1090, 750, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.52 (4, m), 3.75 (2, m), 4.32 (m, 2), 7.17 (5, s); mass spectrum, *m/e* (relative intensity) 207 (51), 206 (24), 176 (10), 174 (10), 164 (15), 130 (6), 122 (18), 121 (100, 104 (22), 91 (18), 86 (19), 77 (37), 58 (15), 51 (18).

From 1.18 g (5.0 mmol) of **9** and 1.21 g (10.00 mmol) of **2** heated for 6 h under N_2, 0.7 g (68%) of **10** was produced. From 1.18 g (5.0 mmol) of **9** and 1.17 g (10.0 mmol) of phenylacetonitrile refluxed for 6 h under N_2, 0.6 g (58%) of **10** was formed.

Registry No.—**1**, 62158-05-8; **2**, 103-67-3; **3**, 622-29-7; **5**, 40753-18-2; **6**, 65943-33-1; **10**, 2032-36-2; **11**, 65943-34-2; *N*-methylthiobenzamide, 5310-14-5; tetramethyl thiophenetetracarboxylate, 6579-15-3; *N*-benzyl-*N*,*N*-dimethylamine, 103-83-3.

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Notes

New Synthesis of 1,3-Dithiole-2-thiones

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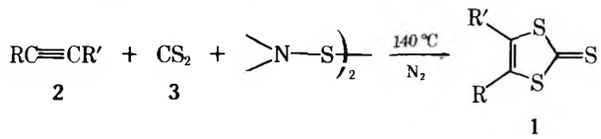
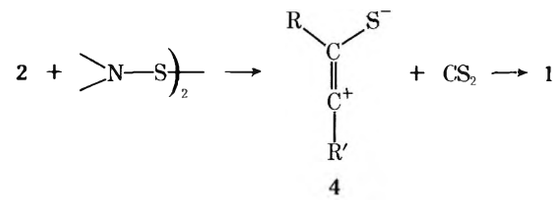
Tetrathiafulvalenes are important components in the formation of charge transfer complexes which have electrical conductance properties similar to those of metals.[1] These compounds are readily prepared[2] from 1,3-dithiole-2-thiones **1**. We now report a new one-step synthesis of **1** from substituted acetylenes **2**, carbon disulfide (**3**), and either



2 3 1

bis(2,2,6,6-tetramethylpiperidine) disulfide or bis(morpholine) disulfide at 140 °C under nitrogen.

Previously we[3] reported that the reactions between **2** and bisamine disulfides led to the formation of thiophenes via the 1,3 dipoles derived from thioketocarbenes.[4] When the reaction of phenylacetylene and the piperidine disulfide was conducted in the presence of carbon disulfide, 4-phenyl-1,3-dithiole-2-thione was formed in 45% yield in addition to a 25% yield of a 3:1 mixture of 2,4- and 2,5-diphenylthiophenes (Table I). We propose[4] that the formation of the dithiole-2-thione arises from 1,3-dipolar cycloaddition between carbon disulfide and the thioketocarbene **4**.



4

In the absence of carbon disulfide, *tert*-butylacetylene reacts with the piperidine disulfide to give sulfur but no thiophene, while in the presence of carbon disulfide 4-*tert*-butyl-1,3-dithiole-2-thione is formed in 41% yield. Thus, the thioketocarbene decomposes to sulfur and *tert*-butylacetylene faster than it undergoes cycloaddition to a second molecule of acetylene to form a thiophene, but it undergoes cycloaddition to carbon disulfide faster than it eliminates sulfur.

Ethyl phenylpropiolate, carbon disulfide, and morpholine disulfide react to give a 99% yield of 4-carboethoxy-5-phenyl-1,3-dithiole-2-thione. However, methyl 1,3-dithiole-2-thione-4-carboxylate and dimethyl 1,3-dithiole-2-thione-4,5-dicarboxylate, derived from methyl propiolate, carbon disulfide, and bis(morpholine) disulfide and from dimethyl acetylenedicarboxylate, carbon disulfide, and the piperidine disulfide, are accompanied by the tetrathiafulvalenes dimethyl [$\Delta^{2,2'}$-bi-1,3-dithiole]-4,4′-dicarboxylate in 10% yield and tetramethyl [$\Delta^{2,2'}$-bi-1,3-dithiole]-4,4′,5,5′-tetracarboxylate in 13% yield, respectively. The dithiole-2-thiones are easily separated from the bidithioles by elution column chromatography.

The formation of these tetrathiafulvalenes suggests an alternative dithiolium carbene mechanism for the reaction producing **1**. Electron-deficient acetylenes are known[5] to react with carbon disulfide to form nucleophilic 1,3-dithiolium carbenes which could undergo displacement at the sulfur in the bisamine disulfides to form an intermediate 1,3-dithiolium cation that collapses to **1**.

Diphenylacetylene failed to react with carbon disulfide and the piperidine disulfide. Since the acetylene does not react with carbon disulfide alone or with the amine disulfide alone to give either a thiophene or sulfur, this lack of reactivity for the acetylene supports neither mechanism more than the other.

However, since electron-rich acetylenes such as 2-butyne do not cycloadd to carbon disulfide and since the *tert*-butyldithiole-2-thione was formed from *tert*-butylacetylene, the thioketocarbene mechanism is more reasonable than the dithiolium carbene mechanism.

A comparison of this method of synthesis with those involving elemental sulfur and metal cation acetylides[6] shows that the latter is limited to monosubstituted acetylenes. The reaction between acetylenes and ethylene trithiocarbonate[11] is limited to electron-deficient acetylenes, while the reaction we report here is not limited in this way.

In conclusion, a simple one-step synthesis of 1,3-dithiole-2-thiones from substituted acetylenes, carbon disulfide, and bisamine disulfides has been demonstrated.

Experimental Section

All boiling points and melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 237 infrared spectrophotometer. NMR spectra were recorded on a Jeol-C-60H spectrometer with Me_4Si as an internal standard. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6 spectrometer with an ionizing potential of 70 eV. Microanalyses were done by Galbraith Laboratory, Inc. Phenylacetylene, ethyl phenylpropiolate, and dimethyl acetylenedicarboxylate were purchased from Aldrich Chemical Co., Inc., and methyl propiolate from Chemical Samples Co. Bis(morpholine) disulfide was bought from ICN Pharmaceuticals, Inc., and recrystallized from ethyl acetate before use. *tert*-Butylacetylene,[7] diphenylacetylene,[8] and bis(2,2,6,6-tetramethylpiperidine) disulfide[9] were prepared according to literature procedures.

General Procedure for the Synthesis of 1. Acetylene **2** and bisamine disulfide in a 4:1 molar ratio were dissolved in 75 mL of **3**, and the resulting solution was placed in a 2-L Parr bomb reactor

Table I. Yields of 1,3-Dithiole-2-thione (1)

RC≡CR′	Registry no.	>N—S→$_2$[a]	Registry no.	Yield of **1**, %	Registry no.
PhC≡CH	536-74-3	A	14045-39-7	45	2314-61-6
$(CH_3)_3CC{\equiv}CH$	917-92-0	A		41	29507-67-3
$PhC{\equiv}CCO_2CH_2CH_3$	2216-94-6	B	103-34-4	99	65818-65-7
$HC{\equiv}CCO_2CH_3$	922-67-8	B		67	55526-01-7
$CH_3O_2CC{\equiv}CCO_2CH_3$	762-42-5	A		33	7396-41-0
PhC≡CPh	501-65-5	A		No reaction	

[a] A: bis(2,2,6,6-tetramethylpiperidine) disulfide. B: bis(morpholine) disulfide.

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equipped with a glass liner. The apparatus was flushed with N_2, sealed, and heated to 140 °C for 24 h. The pressure rose to 140 psi. After cooling, the apparatus was opened, the brown solution was transferred to a round-bottom flask, and the excess carbon disulfide was removed under vacuum. The dark residue was chromatographed over silica gel (30:1 weight ratio of silica gel to mixture) with benzene as eluent. The trithiones 1 are the first materials to elute followed in certain cases by the narrow dark bands corresponding to the tetrathiafulvalenes.

4-Phenyl-1,3-dithiole-2-thione. From 0.41 g (4.0 mmol) of phenylacetylene and 0.34 g (1.0 mmol) of bis(2,2,6,6-tetramethylpiperidine) disulfide, 0.19 g (45%) of trithione was obtained and recrystallized from ethanol: mp 117 °C (lit.[10] mp 117–118 °C); IR (KBr) 3100, 1485, 1445, 1055, 1045, 890, 740, 675 cm^{-1}; NMR (CS_2) δ 6.95 (1, s), 7.32 (5, s); mass spectrum, *m/e* (relative intensity) 210 (76), 134 (100), 121 (13), 102 (14), 91 (24), 90 (23), 77 (14).

4-*tert*-Butyl-1,3-dithiole-2-thione. From 0.33 g (4.0 mmol) of *tert*-butylacetylene and 0.40 g (1.0 mmol) of bis(2,2,6,6-tetramethylpiperidine) disulfide, 1.4 g (99%) of trithione was obtained and recrystallized from diethyl ether: mp 90 °C; IR (KBr) 2980, 1465, 1365, 1250, 1050, 1035, 898, 800, 655 cm^{-1}; NMR (CCl_4) δ 1.33 (9, s), 6.55 (1, s); mass spectrum, *m/e* (relative intensity) 190 (98), 175 (100), 113 (17), 70 (89), 69 (77), 58 (100).

Anal. Calcd for $C_7H_{10}S_3$: C, 44.21; H, 5.26; S, 50.52. Found: C, 44.11; H, 5.43; S, 50.18.

4-Carboethoxy-5-phenyl-1,3-dithiole-2-thione. From 3.48 g (20.0 mmol) of ethyl phenylpropiolate and 1.18 g (5.0 mmol) of bis(morpholine) disulfide, 1.4 g (99%) of trithione was obtained and recrystallized from diethyl ether: mp 92 °C; IR (KBr) 3000, 1740, 1540, 1450, 1260, 1205, 1090, 1080, 1025, 755, 690 cm^{-1}; NMR (CCl_4) δ 1.12 (3, t, J = 8.0 Hz), 4.10 (2, q, J = 8.0 Hz), 7.32 (5, s); mass spectrum, *m/e* (relative intensity) 282 (82), 178 (18), 166 (14), 145 (36), 134 (82), 133 (45), 121 (36), 89 (100), 77 (27).

Anal. Calcd for $C_{12}H_{10}O_2S_3$: C, 51.06; H, 3.54; S, 34.04. Found: C, 51.18; H, 3.64; S, 33.98.

Methyl 1,3-Dithiole-2-thione-4-carboxylate and 4,4′(5′)-Bis(carbomethoxy)-$\Delta^{2,2'}$-bi-1,3-dithiole. From 1.68 g (20.0 mmol) of methyl propiolate and 1.18 g (5.0 mmol) of bis(morpholine) disulfide, 0.63 g (67%) of trithione was obtained and recrystallized from benzene: mp 104 °C; IR (KBr) 3060, 1730, 1560, 1475, 1290, 1200, 1070, 1055, 735 cm^{-1}; NMR (CCl_4) δ 3.88 (3, s), 7.85 (1, s); mass spectrum, *m/e* (relative intensity) 192 (100), 161 (18), 134 (18), 133 (23), 116 (45), 76 (64), 64 (68), 57 (100), 45 (82).

Anal. Calcd for $C_7H_6O_4S_3$: C, 31.25; H, 2.08; S, 50.00. Found: C, 31.47; H, 2.15; S, 49.86.

In addition, 0.16 g (10%) of bidithiole was obtained and recrystallized from ligroin (70–90 °C): mp 240 °C (lit.[11] mp 244–245 °C); IR (KBr) 3080, 1722, 1440, 1250, 1200, 1160, 1050, 939, 829, 765, 730 cm^{-1}; mass spectrum, *m/e* (relative intensity) 320 (100), 204 (68), 161 (29), 105 (36), 101 (32), 76 (59).

Dimethyl 1,3-Dithiole-2-thione-4,5-dicarboxylate and Tetramethyl [$\Delta^{2,2'}$-Bi-1,3-dithiole]-4,4′,5,5′-tetracarboxylate. From 1.14 g (8.0 mmol) of dimethyl acetylenedicarboxylate and 0.69 g (2.0 mmol) of bis(2,2,6,6-tetramethylpiperidine) disulfide, 0.17 g (33%) of trithione was obtained and recrystallized from a mixture of toluene and hexane: mp 89 °C (lit.[11] mp 87 °C): IR (KBr) 1750, 1725, 1550, 1425, 1250, 1100, 1085, 1010, 920, 760 cm^{-1}; NMR (CCl_4) δ 3.86 (s); mass spectrum, *m/e* (relative intensity) 250 (100), 219 (22), 191 (22), 174 (26), 107 (48), 76 (49), 59 (96), 45 (28).

In addition, 0.11 g (13%) of bidithiole was obtained and recrystallized from methanol: mp 169–170 °C (lit.[5] mp 169–170 °C); IR (KBr) 1740, 1710, 1570, 1440, 1262, 1020 cm^{-1}; NMR (CCl_4) δ 3.85 (s); mass spectrum, *m/e* (relative intensity) 436 (100), 404 (11), 377 (30), 332 (22), 261 (50), 100 (17), 88 (44), 59 (55), 44 (44).

Registry No.—**3**, 75-15-0; 4,4′(5′)-bis(carbomethoxy)-$\Delta^{2,2'}$-bi-1,3-dithiole, 51751-18-9; tetramethyl [$\Delta^{2,2'}$-bi-1,3-dithiole]-4,4′,-5,5′-tetracarboxylate, 26314-39-6.

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Phthalimido Phenylcarbamate: A New Isocyanate Generator

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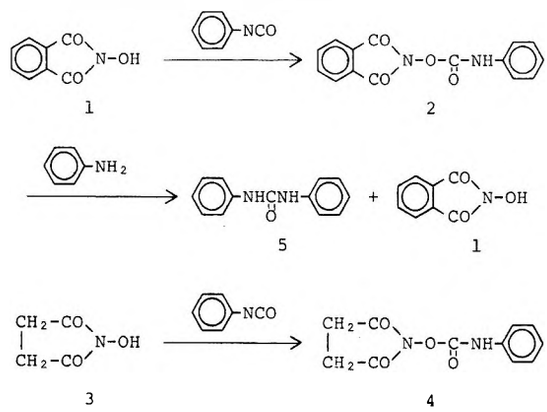
N-Hydroxyphthalimide (**1**) is an interesting compound as it has a unique acidic hydroxy group, and its alkylation[1-6] and esterification[7,8] have been reported in the literature. Regarding other reactions of **1**, however, very little has been published. As a result of our current interest in reactions of imide derivatives, we have recently examined the reaction of **1** with phenyl isocyanate. The reaction gives rise to the formation of a new type of urethane linkage which is expected to regenerate phenyl isocyanate on heating. The urethane compound would be a relatively stable solid which could be more easily handled with safety than the isocyanate, and moreover it could form a stable mixture with nucleophiles in solid state at ambient temperatures. These properties are especially useful in coating chemistry. We now wish to report the synthesis of phthalimido phenylcarbamate (**2**) and its potential as an isocyanate generator, comparing them with those of succinimido phenylcarbamate (**4**).



The carbamate **2** was prepared from *N*-hydroxyphthalimide (**1**) and phenyl isocyanate in dry dioxane or dimethylacetamide. The succinimide derivative **4** was synthesized from *N*-hydroxysuccinimide (**3**) similarly.

The thermal stability of **2** was examined by means of thermogravimetric analysis at a heating rate of 5 °C/min in air, and it was found that **2** decomposed with two-step weight loss. The first weight loss observed between 97 and 170 °C accounted for 45% of the initial weight, which was in good agreement with the theoretical value (42%) for the loss of phenyl isocyanate. The infrared spectrum of the solid obtained after the first weight loss was identical with that of the authentic **1**. Compound **2** was therefore thought to start regenerating phenyl isocyanate from around 100 °C in the solid state. Compound **4**, on the other hand, showed no two-step weight loss, probably on account of the volatility of the decomposed species. The weight loss started at 129 °C.

In order to evaluate its potential as an isocyanate generator, **2** was subjected to reaction with aniline at various temperatures. A dichloromethane solution containing equimolar amounts of **2** and aniline started to deposit diphenylurea (**5**) after about 4 h at room temperature (ca. 25 °C). Under these

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Table I. Reaction of 2 or 4 with Aniline

Solvent (bp, °C)	Reaction time, h	Reaction of 2 yield, % 5	1	Reaction of 4 yield, % 5	3
Dioxane (101)	4	96	90	89	54
Benzene (80)	4	85	86	98	45
Acetone (56)	4	84	90	89	36
Dichloromethane (40)	10	42	*a*	73	*b*

[a] A mixture of 1 and unreacted 2 was obtained. [b] A mixture of 3 and unreacted 4 was obtained.

conditions, **5** was isolated in 5% yield after 48 h. The reaction was then carried out in dioxane, benzene, acetone, and dichloromethane at their boiling temperatures, and the products, diphenylurea (**5**) and *N*-hydroxyphthalimide (**1**), were isolated by fractional recrystallization. Table I summarizes the results of the reactions in the four solvents. Compound **4** was similarly treated with aniline, and the results are included in Table I. As shown in the table, **5** was isolated in good yield from **2** in dioxane, benzene, or acetone despite the small scale reaction. When dichloromethane was used as a solvent, however, the yield of **5** was much lower and a mixture of **1** and unreacted **2** was obtained, presumably because of the low boiling temperature of the solvent. Compound **4** also gave **5** in good yield, even in dichloromethane, which suggests that **4** is more reactive toward aniline than **2**.

The reactivity of **2** and **4** was then compared by the reaction of equimolar amounts of **2**, **4**, and aniline. After repeated fractional recrystallization, the expected five compounds were isolated in yields as follows: **5**, 96%; **1**, 39%; **3**, 30%; **2**, 48%; and **4**, 30%. The fact that more **2** was recovered than **4** seems to support the idea that **4** is more reactive than **2**, though the isolated amount of **3** is less than that of **1** due to the difficulty in recrystallization of **3**.[9] This is in good accordance with the tendency of a compound with a more acidic leaving component to show better reactivity in the amide-forming nucleophilic substitution reaction;[10] pK_a values of **1** and **3** are 7.0[11] and 6.0,[12] respectively. Although both **2** and **4** were thus shown to be good isocyanate generators, **2** was considered to be a better one in terms of the ease in recovering the starting *N*-hydroxy compound.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Jasco IR-G spectrometer. NMR spectra were obtained on Jeol JNM-MH-60 or Hitachi R-24 spectrometers. Elemental analyses were performed by Shonan Bunseki Center, Kanagawa, Japan.

Materials. *N*-Hydroxyphthalimide (**1**) was prepared according to the procedure reported by Mazur and Plume.[13] *N*-Hydroxysuccinimide (**3**) was synthesized by the method of Anderson, Zimmerman, and Callahan.[14] All of the solvents that were used were dried by the usual manner.

Phthalimido Phenylcarbamate (2). To a solution of 1.14 g (7 mmol) of **1** in 20 mL of dry dioxane was added 0.76 mL (0.83 g, 7 mmol) of phenyl isocyanate and then a drop of dibutyltin dilaurate as catalyst. The solution was stirred at room temperature, and precipitation began to take place in 4 h. The stirring was discontinued after 6 h, and the solvent was removed under reduced pressure. The resulting crystalline solid was recrystallized from dichloromethane–petroleum ether to give 1.86 g (94%) of colorless granular crystals. On rapid heating, **2** melted at 175–178 °C: IR (KBr) 3240, 1775, and 1735 cm^{-1}; NMR (Me_2SO-d_6) δ 6.90–7.50 (m, 5, C_6H_5–N), 7.75–7.90 (m, 4, $C_6H_4(CO)_2N$), and 8.45 (broad s, 1, NH). Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 64.22; H, 3.80; N, 9.68.

Succinimido Phenylcarbamate (4). Starting from 0.806 g (7 mmol) of *N*-hydroxysuccinimide and 0.75 mL (0.83 g, 7 mmol) of phenyl isocyanate, 1.41 g (86%) of **4** was obtained as colorless plates after recrystallization from chloroform–petroleum ether. On rapid heating, **4** melted at 149–154 °C; IR (KBr) 3240, 1775, and 1715 cm^{-1}; NMR (Me_2SO-d_6) δ 2.75 (s, 4, CH_2CH_2), 6.93–7.43 (m, 5, C_6H_5), and 7.45 (broad s, 1, NH). Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.12; H, 4.20; N, 12.13.

Reaction of 2 and Aniline. To a solution of 0.846 g (3 mmol) of **2** in 8 mL of dry acetone was added 0.285 mL (0.29 g, 3.1 mmol) of aniline. The solution was heated at reflux for 4 h and evaporated under reduced pressure to give a slightly yellow solid. It was washed with petroleum ether to remove the unreacted aniline and then recrystallized from dioxane to give 0.51 g of **5** as colorless needles. The filtrate was concentrated under reduced pressure, and the residual solid was fractionally recrystallized from dioxane–petroleum ether to give an additional 0.05 g of **5**, 0.08 g of a mixture of **5** and **1**, and 0.44 g (90%) of **1**. The total yield of **5** was 0.56 g (84%), mp 241–242 °C (lit.[15] mp 241–242 °C).

Succinimide derivative **4** was treated with aniline in the same way. The dried mixture was washed with water to remove **3**, which was recrystallized from ethyl acetate.

Reaction of a Mixture of 2 and 4 with Aniline. To a solution of 0.846 g (3 mmol) of **2** and 0.703 g (3 mmol) of **4** in 8 mL of dry acetone was added 0.273 mL (0.279 g, 3 mmol) of aniline. After heating the solution for 4 h, the solvent was removed under reduced pressure. The residual solid was fractionally recrystallized from chloroform–hexane to give 0.608 g (96%) of **5**, 0.189 g (39%) of **1**, 0.105 g (30%) of **3**, 0.403 g (48%) of **2**, and 0.211 g (30%) of **4**.

Registry No.—**1**, 524-38-9; **2**, 60506-34-5; **3**, 6066-82-6; **4**, 23583-11-1; **5**, 102-07-8; phenyl isocyanate, 103-71-9; aniline, 62-53-3.

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Oxidative Acetoxylation of Anisole by Ceric Ammonium Nitrate in Acetic Acid[1]

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Substitution of hydrogen atoms in aromatic compounds by acyloxy groups via oxidative routes is being given considerable attention in view of the mechanistic implication as well as of the synthetic potential.[2,3]

We have shown that ceric ammonium nitrate (CAN) in acetic acid is a suitable reagent for the functionalization of polymethylbenzenes.[4] Substitution of benzylic C–H bonds was the only reaction observed with all the substrates investigated, with the sole exception of mesitylene, for which nu-

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Table I. Kinetic Data for the Reaction of Anisole with CAN in Acetic Acid at 40 °C[a]

[Anisole], M	[CAN], ×10⁴ M	$t_{5\%}$ × [anisole], s M[b]	[NH_4NO_3], ×10² M	[$Ce^{III}(NO_3)_3$], ×10⁴ M
0.101	12.9	75 ± 10		
0.0203	12.9	74 ± 5		
0.0101	12.9	79 ± 5		
0.103	12.9	28 ± 2	2.02	
0.102	1.26	25 ± 2	2.02	
0.104	12.9	410 ± 70	2.02	16.2
0.104	6.44	440 ± 50	2.02	16.2
0.104	3.22	440 ± 50	2.02	16.2
0.104	1.29	490 ± 70	2.02	16.2
0.111	1.29	155 ± 10	2.02	4.05
0.114	1.29	790 ± 100	2.02	29.7

[a] In the absence of light and of oxygen. [b] Time at 5% of reaction ($t_{5\%}$) multiplied by the concentration of anisole. Each value is the average of three determinations.

clear acetoxylation also occurred as a side reaction. We now wish to report that with anisole, i.e., an electron-rich aromatic substrate bearing no benzylic C–H bonds, CAN in AcOH smoothly promotes nuclear acetoxylation.

Results and Discussion

A homogeneous solution in AcOH of anisole and CAN was kept at 40 °C under nitrogen and in the dark for 22 h. VPC analysis of the crude product showed the presence of *o*- and *p*-acetoxyanisole whereas no peak attributable to the meta isomer was observed. The two acetoxyanisoles were also isolated in a pure form by means of preparative VPC. In order to allow for the possible further oxidation of initially formed reaction products,[5] the isomer distribution was determined by VPC at different times in the early stages of the reaction. It was found that the ortho/para ratio remains unchanged up to ca. 30% reaction, the average value being 0.81 ± 0.03. Thus the ortho/para ratio appears unaffected by further oxidation of the two isomers.

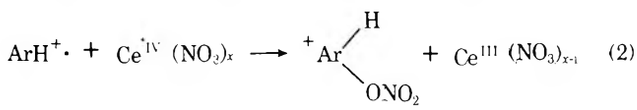
The determination of the times at 5% of reaction revealed that the reaction is approximately first order in anisole and in CAN[7] and has an order −1 in Ce(III). The experiments in which the concentrations of Ce(IV) or Ce(III) were changed were generally carried out in the presence of an excess of NH_4NO_3 in order to keep the total salt concentration practically constant. The addition of NH_4NO_3, which was the salt of choice since its anion is also the ligand in the oxidizing complex, exerts a significant acceleration of the reaction rate as already observed in other oxidation reactions by CAN.[4a,8] All kinetic results are reported in Table I. The results, together with the well-known ability of Ce(IV) compounds to act as one-electron transfer reagents toward electron-rich aromatic compounds,[10] allow us to suggest that the reaction of Ce(IV) with anisole leads to the formation, in a fast and reversible step, of a radical cation which then slowly decomposes to products (eq 1).

$$ArH + Ce^{IV} \rightleftharpoons ArH^{+\cdot} + Ce^{III} \quad (1a)$$

$$ArH^{+\cdot} \xrightarrow[\text{more than one step}]{\text{slow}} \text{products} \quad (1b)$$

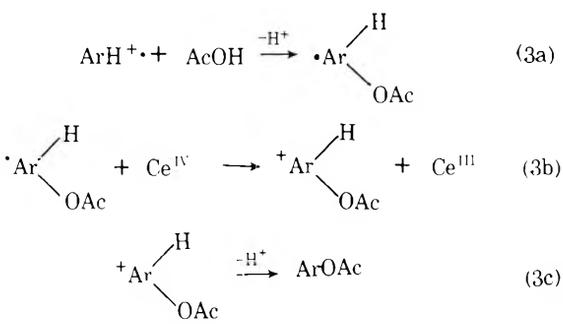
This suggestion is also supported by the fact that our kinetic pattern is practically identical to that observed in the Mn(III) induced acetoxylation of 1-methoxynaphthalene, for which a mechanism similar to that reported in eq 1 has been proposed.[11]

As to the rate-limiting transformation of the radical cation into products, a reaction with either a nucleophile or a radical (either as a free species or bound to a carrier) could in principle be envisaged. However, the observation of a first-order reaction in Ce(IV) and the absence of aryl nitrates and/or decomposition products possibly derived therefrom[12] rules out the operation of a ligand transfer reaction (eq 2)



$$ArH^{+\cdot} + Ce^{IV}(NO_3)_x \longrightarrow {}^{+}Ar(H)(ONO_2) + Ce^{III}(NO_3)_{x-1} \quad (2)$$

and strongly suggests the intervention of the mechanism of eq 3



$$ArH^{+\cdot} + AcOH \xrightarrow{-H^+} {}^{\cdot}Ar(H)(OAc) \quad (3a)$$

$${}^{\cdot}Ar(H)(OAc) + Ce^{IV} \longrightarrow {}^{+}Ar(H)(OAc) + Ce^{III} \quad (3b)$$

$${}^{+}Ar(H)(OAc) \xrightarrow{-H^+} ArOAc \quad (3c)$$

where a nucleophilic attack by the solvent AcOH affords a radical intermediate, which in turn can be easily oxidized by Ce(IV) to a cationic σ complex.

Interestingly, the isomer distribution in the oxidation of anisole by CAN/AcOH appears to follow the odd-electron density distribution at the various positions of the anisole radical cation.[10] The positional selectivity is higher than that reported for related oxidative acetoxylation reactions of anisole (see Table II, lines 2–5) for which, however, without a kinetic support, a nucleophilic attack of acetate ion on the radical cation has been suggested. In the latter reactions appreciable amounts of the meta isomer are formed, and the ortho/para ratio approaches the statistical value of 2. The different behavior can be accounted for by operation of the reactivity–selectivity principle, according to which the neutral, less-reactive, nucleophile AcOH is expected to exhibit increased selectivity as compared with the stronger nucleophile AcO^-. A similar view has been presented to account for different ortho/para ratios in a comparison of cyanation, acetoxylation, and trifluoroacetoxylation of the chlorobenzene radical cation.[16]

The isomer distribution of the reaction promoted by CAN is also significantly different from that exhibited in the reactions induced by $Pb(OAc)_4$ in AcOH (Table II, line 6). However, in the latter case the products of nuclear acetoxylation have been suggested to derive from the collapse of the radical cation and the associated lead species.

Table II. Isomer Distribution in Different Oxidative Acetoxylation Reactions of Anisole

Oxidizing system	Isomer distribution, % Ortho	Meta	Para	Ortho/para ratio
CAN, AcOH[a]	45		55	0.82
$Ag(bpy)_2S_2O_8$, AcOH, AcONa 0.5 M[b]	68	1	31	2.19
Anodic oxidation, AcOH, AcONa 1.0 M[c]	67.4	3.5	29.1	2.31
AcONa 0.3 M	57.3	3.2	39.5	1.45
AcONa 0.1 M	60.2	2.2	37.6	1.60
$Pb(OAc)_4$, AcOH[d]	18		82	0.22

[a] This work. [b] Reference 13. [c] Reference 14. [d] Reference 15 (a 5:95 ortho/para ratio is obtained when the reaction is carried out in the presence of air.

Experimental Section

Proton magnetic resonance spectra were taken on a Jeol JNM-C6OHL spectrometer, using Me_4Si as the internal standard. Infrared spectra were obtained on a Perkin-Elmer 257 from 2% solutions in CCl_4. VPC analyses were performed on a GI Fractovap (C. Erba). UV spectra and kinetics were recorded with a Beckman DBGT spectrophotometer.

Materials. Ceric ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$ (Schuchardt, 99.9% pure) was dried at 85 °C for 1 h. Acetic acid (C. Erba 99.8% pure) was thoroughly fluxed with pure nitrogen before use. Ammonium nitrate (C. Erba, 99% pure), cerous nitrate $[Ce(NO_3)_3 \cdot 6H_2O]$ (C. Erba, 98% pure), anisole (C. Erba, 99% pure), *m*-methoxyphenol (Merck, 97% pure), and *p*-methoxyphenol (C. Erba, 99% pure) were commercial samples and were used as received. *o*-Methoxyphenol (Farmitalia) was distilled before use.

Methoxyphenyl Acetates. The three acetate isomers were prepared by acetylation of the corresponding phenol with acetic anhydride and acqueous alkali. Complete resolution of a mixture of the three isomers was achieved by VPC on a 1-m column, packed with 10% LAC 728, operating at 110 °C.

The Oxidation of Anisole with CAN. In a typical experiment, anisole (9.2 mmol) in 50 mL of oxygen-free acetic acid was added to a homogeneous solution of CAN (4.6 mmol) in 200 mL of the same solvent. The mixture was kept at 40 °C under nitrogen in a dark place. After 22 h (75% of Ce(IV) consumed) the reaction mixture was poured into cold ethyl ether and washed with water. After removing the solvent, the residue, which showed strong carbonyl absorption at 1770 cm^{-1}, was analyzed by VPC. Comparison of the gas chromatogram with those of authentic samples of the three isomeric acetoxyanisoles showed that *o*- and *p*-acetoxyanisole accounted for more than 95% of the reaction products, as based on peak areas. The two acetoxyanisoles were also isolated from a product mixture by means of preparative VPC on a 2-m column packed with SE 30 10% operating at 100 °C and compared with the authentic samples. No peak attributable to the meta isomer was present in the gas chromatogram thus indicating that this isomer, if present, is less than 0.5%.

Kinetic Measurements. The rates of oxidation of anisole were measured by following the disappearance of cerium(IV) in a thermostated cell compartment of a UV spectrophotometer. The optical densities were determined at 410 nm (ϵ 6.2×10^2 M^{-1} cm^{-1}) and in the presence of NH_4NO_3 at 360 (ϵ 4.1×10^3 M^{-1} cm^{-1}), 390 (ϵ 14.9×10^2 M^{-1} cm^{-1}), and 410 nm (ϵ 7.5×10^2 M^{-1} cm^{-1}) depending on the concentration of CAN.

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Registry No.—CAN, 16774-21-3; anisole, 100-66-3; *o*-acetoxyanisole, 613-70-7; *m*-acetoxyanisole, 5451-83-2; *p*-acetoxyanisole, 1200-06-2; acetic acid, 64-19-7.

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A New, Mild Method for the Synthesis of Azo Compounds

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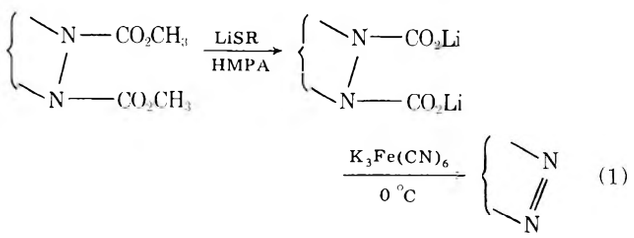
Azo compounds have long played a significant role in the development of mechanistic[1] and synthetic[2] organic chemistry. Often, however, their synthesis is encumbered by the harsh conditions of their genesis. Most methods involve the conversion of a dicarbamate to an hydrazo compound followed by oxidation to afford the desired azo linkage. While alkaline saponification of the dicarbamate at temperatures exceeding 80 °C has frequently been used,[3] in many cases only the most robust compounds survive these harsh conditions. The reductive cleavage of bis(2,2,2-trichloroethyl) esters,[4] the hydrogenolysis of benzyl esters,[5] and the β-elimination of β-tosylethyl esters[6] represent mild alternatives to alkaline saponification. Still, we have uncovered examples where even the conditions of these milder methods have proven to be incompatible with the survival of the desired product.[7]

We now wish to report that we have discovered a mild, one-pot, two-step sequence to effect the conversion of a dicarbamate to an azo linkage.[8] The conversion is effected at or below room temperature and in yields ranging from 60 to 80%; the often-times unstable hydrazo compound which is produced in most methods is bypassed entirely. The low temperatures required to effect the sequence make it possible to isolate even thermally labile azo compounds.

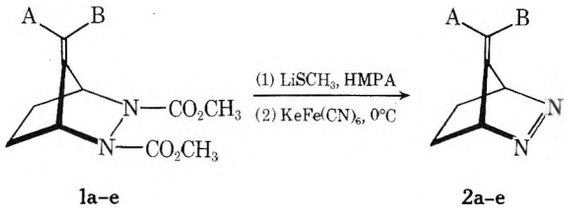
The method, outlined in eq 1, involves the room temperature mercaptide-induced nucleophilic cleavage of a dimethyl dicarbamate to afford a dilithium dicarboxylate. Oxidation with aqueous potassium ferricyanide at 0 °C results in the immediate evolution of gas (CO_2) and the formation of yellow Fe(II) salts.[9,10] Both the lithium salts of *n*-propyl mercaptan and methyl mercaptan have been successfully utilized. These reagents, 0.5–1.3 M in HMPA, are easily prepared and can be stored in the refrigerator for at least 1 month without showing



(1)

0022-3263/78/1943-2921$01.00/0

Table I



1a–e 2a–e

Registry no.	Entry	A	B	Reaction time: Cleavage,[a] h	Reaction time: Oxidation,[b] h	Yield,[c] %	Registry no.
66322-83-6	**1a**	CH_3	CH_3	4	1	65	31689-32-4
66322-84-7	**1b**	$-(CH_2)_5-$		3	1	72	66322-88-1
66322-85-8	**1c**	H	Cl	12	1	62	66322-89-2
66322-86-9	**1d**	Ph	Ph	16	1	82	66322-90-5
66322-87-0	**1e**	C_2H_5	C_2H_5	16	1	75	66322-91-6

[a] Room temperature. [b] 0 °C. [c] Isolated yield.

appreciable deterioration. We prefer to use the lithium salt of methyl mercaptan since the byproduct of the cleavage reaction, dimethyl sulfide, can easily be removed (bp 37 °C).

We have applied this sequence to the synthesis of a variety of bicyclic azo compounds; the results are summarized in Table I.

In a typical procedure, 1.48 mmol of a dicarbamate (**1a–e**) is added to 4.46 mmol of lithium methyl mercaptide (1.2 M in HMPA). After stirring for 3–18 h (note Table I) at room temperature, the reaction mixture is cooled to 0 °C, 4.46 mmol of potassium ferricyanide in 20 mL of water is added, and stirring is continued for another hour. After washing with pH 6 brine, extraction with pentane, and crystallization, the azo compounds **2a–e** are obtained in 60–80% yield.

Because of our interest in the chemistry of bicyclic azo compounds, we have focused attention upon their synthesis. We feel that the method is of sufficient generality to be applicable to a wide range of systems.[11]

Experimental Section

^{1}H NMR spectra were obtained using a Varian T-60 spectrometer. The spectral data are reported in δ relative to Me_4Si as an internal standard and $CDCl_3$ as solvent. All reactions were performed under a nitrogen atmosphere. Each of the azo compounds synthesized in this study are known compounds; therefore, combustion analyses were not run.

Materials. Methyl mercaptan (Linde) was used directly from a lecture bottle. Hexamethylphosphoramide (Aldrich) was vacuum distilled from barium oxide into a receiver containing 4A molecular sieves (Linde). The distilled solvent was then purged of oxygen by repeated freeze–thaw cycles. The dicarbamates **1a–e** were prepared by known sequences.[3b]

Lithium Methyl Mercaptide. Methyl mercaptan (25 mL, 0.45 mol) was condensed directly into a glass jacketed distilling reservoir which was cooled by passing cold nitrogen (−130 °C) through the receiver jacket. The mercaptan was then added dropwise to a precooled (0 °C) 250-mL three-neck flask equipped with a single-piece nitrogen inlet vacuum-take-off tube and a coarse glass-frit filtration adapter and charged with 3.30 g (0.42 mol) of lithium hydride in 150 mL of HMPA. The reaction was allowed to proceed for 1 h. The gas-condensing reservoir was then removed under a vigorous stream of nitrogen, the reaction vessel quickly stoppered, the system alternately purged with nitrogen and evacuated, and the reagent then filtered with the aid of a vacuum into a one-neck 250-mL flask attached to the filtration adapter. Upon completion of the transfer, the flask was stoppered with a serum cap, then alternately evacuated and purged with nitrogen, and finally stored in the refrigerator under nitrogen until ready for use. Titration to a phenolphthalein end point gave a value of 1.2 M (we have encountered a range of 1.0 to 1.3 M).

Azo Compounds 2a–e. Only a procedure for the diphenylazo compound **2d** is presented in detail. The synthesis of the other azo compounds is achieved in the same way using the appropriate modifications in reaction time as noted in the text.

Lithium methyl mercaptide (2.10 mmol, 1.2 M in HMPA) was added via syringe to a nitrogen-purged 50 mL one-neck flask equipped with a magnetic stirring bar, a 60-mL addition funnel, and a nitrogen inlet tube and charged with 0.26 g (0.68 mmol) of **1d.** The reaction was allowed to proceed at room temperature for 16 h, at which time the solution was cooled to 0 °C and 0.68 g (2.10 mmol) of potassium ferricyanide dissolved in 20 mL of water was added dropwise; immediate precipitation of yellow salts and gas evolution were noted. The decarboxylation was allowed to proceed for 1 h, and the resulting mixture was then added to 125 mL of pH 6 brine and extracted six times with 100 mL each of pentane. The combined pentane extracts were then washed twice with 300 mL each of pH 6 brine, dried over magnesium sulfate, and concentrated in vacuo to afford 147 mg (82%) of **2d.**

^{1}H NMR Data for 2a–e. 2a: δ 5.37 (broad q, 2 H, bridgeheads), 1.63 (s, 6 H, CH_3), 1.0–1.7 (m, 4 H, $-CH_2-$). **2b:** δ 5.39 (broad q, 2 H, bridgeheads), 1.9–2.2 (m, 4 H, allylic CH_2), 1.32–1.68 (m, 6 H, cyclohexyl CH_2), 1.32–1.68 (buried under cyclohexyl methylenes), 0.95–1.2 (broad m, 4 H, ethanobridge). **2c:** δ 5.76 (broad s, 1 H, HCCl=C<), 5.50 (broad s, 1 H, bridgehead), 5.20 (broad s, 1 H, bridgehead), 1.05–1.80 (broad m, 4 H, $-CH_2-$). **2d:** δ 6.98–7.38 (m, 10 H, Ph), 5.39 (broad q, 2 H, bridgeheads), 1.69–1.92 (m, 2 H, $-CH_2-$), 1.05–1.32 (m, 2 H, $-CH_2-$). **2e:** 5.32 (broad q, 2 H, bridgehead), 2.0 (q, 4 H, CH_2CH_3), 0.98 (t, 6 H, CH_2CH_3), 0.8–1.30 (m, 4 H, ethano bridge).

Acknowledgment. We are grateful to the Public Health Service (Grant No. CA21144-01), the Cancer Research Coordinating Committee of the University of California, and the UCSB Committee on Research for support of this research. M.V. thanks the University of California for a Campus fellowship.

Registry No.—Lithium methyl mercaptide, 35638-70-1.

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(1) A few examples include (a) P. B. Dervan and T. Uyehara, *J. Am. Chem. Soc.*, **98,** 1262 (1976); (b) J. A. Berson and S. S. Olin, *ibid.*, **91,** 777 (1969); and (c) H. E. Zimmerman, R. J. Boettcher, N. E. Buehler, G. E. Keck, and M. G. Steinmetz, *ibid.*, **98,** 7680 (1976).
(2) For examples see inter alia (a) B. M. Trost, R. M. Cory, P. H. Scudder, and H. B. Neubold, *J. Am. Chem. Soc.*, **95,** 7813 (1973); and (b) T. J. Katz and N. Acton, *ibid.*, **95,** 2738 (1973).
(3) See inter alia (a) P. G. Gassman and K. H. Mansfield, *Org. Synth.*, **49,** 1 (1969); and (b) J. A. Berson, R. J. Bushby, J. M. McBride, and M. J. Tremelling, *J. Am. Chem. Soc.*, **93,** 1544 (1971).
(4) M. F. Semmelhack, J. S. Foos, and S. Katz, *J. Am. Chem. Soc.*, **95,** 7325 (1973).
(5) M. A. Heyman and J. P. Snyder, *Tetrahedron Lett.*, 2859 (1973).
(6) S. Masamune, N. Nakamura, and J. Spadara, *J. Am. Chem. Soc.*, **97,** 918 (1975).
(7) Unpublished work of M. G. Venegas and A. Bukhari, University of California, Santa Barbara, Calif.
(8) The dicarbamates were synthesized by Diels–Alder reaction of the appropriate fulvene with dimethyl azodicarboxylate followed by selective monohydrogenation. The authors wish to thank L. Dang and G. Muller for samples of two of the fulvenes.
(9) J. McMurry, *Org. React.*, **24,** 187 (1976).
(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, pp 929–933.

(11) Potassium ferricyanide has previously been used to convert *vic*-1,2-dicarboxylate groups to double bonds. See, for example, L. F. Fieser and M. J. Haddadin, *J. Am. Chem. Soc.*, **86**, 2392 (1964). The oxidative decarboxylation of 1,2-dicarboxylic acids is, of course, a well-known process. See inter alia (a) C. A. Grob, M. Ohta, and A. Weiss, *Helv. Chim. Acta*, **41**, 1911 (1958); and (b) E. N. Cain, R. Vukov, and S. Masamune, *J. Chem. Soc. D*, 98 (1969).

Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution

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Received January 26, 1978

We wish to describe a simple absorption chromatography technique for the routine purification of organic compounds. Large scale preparative separations are traditionally carried out by tedious long column chromatography. Although the results are sometimes satisfactory, the technique is always time consuming and frequently gives poor recovery due to band tailing. These problems are especially acute when samples of greater than 1 or 2 g must be separated. In recent years several preparative systems have evolved which reduce separation times to 1–3 h and allow the resolution of components having $\Delta R_f \geq 0.05$ on analytical TLC. Of these, medium pressure chromatography[1] and short column chromatography[2] have been the most successful in our laboratory. We have recently developed a substantially faster technique for the routine purification of reaction products which we call flash chromatography. Although its resolution is only moderate ($\Delta R_f \geq 0.15$), the system is extremely inexpensive to set up and operate and allows separations of samples weighing 0.01–10.0 g[3] in 10–15 min.[4]

Flash chromatography is basically an air pressure driven hybrid of medium pressure and short column chromatography which has been optimized for particularly rapid separations. Optimization studies were carried out under a set of standard conditions[5] using samples of benzyl alcohol on a 20 mm × 5 in. column of silica gel 60 and monitoring the column output with a Tracor 970 ultraviolet detector. Resolution is measured in terms of the ratio of retention time (r) to peak width (w,$w/2$) (Figure 1), and the results are diagrammed in Figures 2–4 for variations in silica gel particle size, eluant flow rate, and sample size.

A number of interesting facts emerge from these data. First, we find that one of the most popular grades of silica gel 60, 70–230 mesh (63–200 μm), gives the poorest resolution of any gel studied under our standard conditions. Second, particle sizes less than 40 μm offer no improvement in resolution with our method of packing.[7] Column performance is quite sensitive to the rate of elution and is best with relatively high eluant flow rates. The solvent head above the adsorbent bed should drop 2.0 ± 0.1 in./min for optimum resolution with mixtures of ethyl acetate/petroleum ether (30–60 °C).[8] Finally, the peak width shows the expected increase with the sample size. Sample recovery was ≥95%.

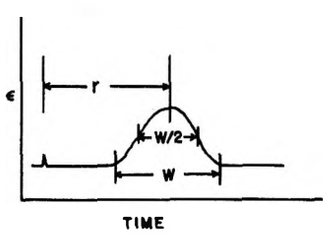

Figure 1. Typical chromatogram.

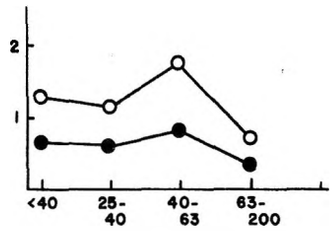

Figure 2. Silica gel particle size[6] (μm): (●) r/w; (○) $r/(w/2)$.

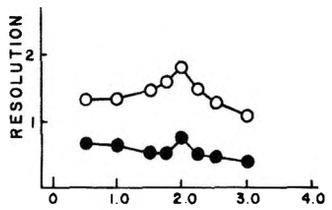

Figure 3. Eluant flow rate (in./min).

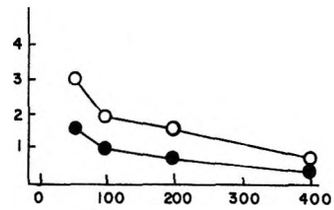

Figure 4. Sample size (mg).

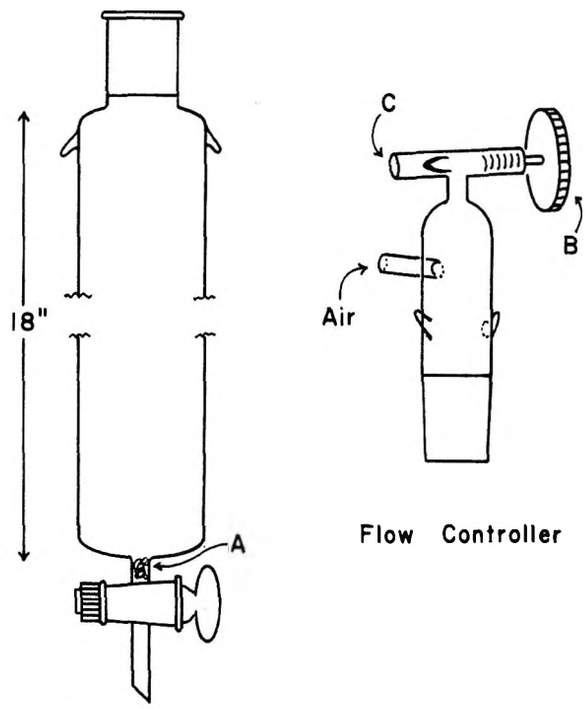

Figure 5.

The apparatus required for this technique consists of a set of chromatography columns and a flow controller valve (below). The column is a flattened bottom 18 in. glass tube fitted with a Teflon stopcock and topped with a 24/40 glass joint. Columns without fritted glass bed supports are generally preferred since they have significantly less dead volume than the standard fritted round-bottom variety. The flow controller

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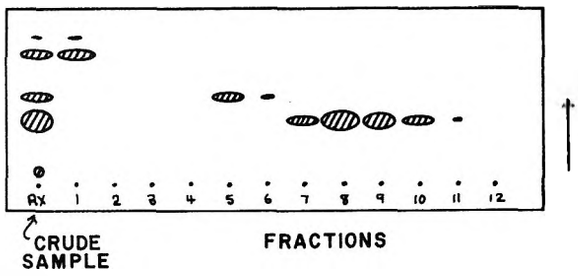


Figure 6.

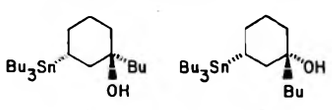
valve is a simple variable bleed device for precise regulation of the elution rate and is constructed from a glass/Teflon needle valve (Ace Glass Co. No. 8193-04 or equivalent) and a standard 24/40 joint.

A detailed procedure is presented in the experimental section and is summarized as follows: (1) A solvent is chosen which gives good separation and moves the desired component to R_f = 0.35 on analytical TLC (E. Merck No. 5765).[9] (2) A column of the appropriate diameter (see Table I) is selected and filled with 5–6 in. of dry 40–63 μm silica gel (E. Merck No. 9385).[10] (3) The column is filled with solvent and pressure is used to rapidly push all the air from the silica gel. (4) The sample is applied and the column is refilled with solvent and eluted at a flow rate of 2 in./min.

The time required to elute the desired components from the column is generally so fast (5–10 min) that we have abandoned automatic fraction collectors in favor of a simple rack holding forty 20 × 150 mm test tubes. Small fractions are typically collected early in the elution with larger ones being collected toward the end of the chromatography. Separated components are conveniently detected by spotting ~5 μL of each fraction along the long side of 7 cm × 2.5 cm TLC plate and then by developing the plate sideways. Heavier spotting may be required for small samples or highly retentive components. A typical separation is shown in Figure 6.

Over the past year we have run many hundreds of these columns. In every case we have been able to effect clean separation of compounds having $\Delta R_f \geq 0.15$ in less than 15 min and in many cases separations at $\Delta R_f \simeq 0.10$ were possible. The amount of sample used on a given column is proportional to its cross-sectional area and Table I can serve as a guide to column selection.

The sample size may increase substantially if less resolution is required; we have used a 50-mm column for the purification of up to 10 g of compound having impurities at $\Delta R_f \geq 0.4$. Resolution is maintained even with large diameter columns. For example the epimeric alcohols 1 and 2 have an R_f of 0.34



1 2

and 0.25, respectively, in 5% ethyl acetate/petroleum ether. A 1.0-g mixture of 1 and 2 (ΔR_f = 0.09) easily separated with only a 65-mg mixed fraction in 7 min on a 40-mm diameter column (500 mL of 5% EtOAc/petroleum ether).

If the components to be separated are closer on TLC than ΔR_f 0.15, increased resolution may be achieved by using a longer (e.g., 10 in.) column of gel alternatively a less polar solvent can be used. Such a solvent can be selected to move the desired components on TLC to R_f = 0.25 without increasing the elution times too drastically. In either case, the column should be only lightly loaded with sample and a rapid flow rate of 2 in./min should be maintained. Slower flows clearly give poorer resolution with ethyl acetate/petroleum ether mixtures.

Table I

column diameter, mm	vol of eluant,[a] mL	sample: typical loading (mg) $\Delta R_f \geq 0.2$	sample: typical loading (mg) $\Delta R_f \geq 0.1$	typical fraction size, mL
10	100	100	40	5
20	200	400	160	10
30	400	900	360	20
40	600	1600	600	30
50	1000	2500	1000	50

[a] Typical volume of eluant required for packing and elution.

In conclusion, flash chromatography provides a rapid and inexpensive general method for the preparative separation of mixtures requiring only moderate resolution. Even in cases where high resolution is required, preliminary purification by the flash technique allows simplified high-resolution separations without contamination of expensive HPLC columns. Finally, we would like to stress the facts that use of the 40–63 μm silica gel and a pressure- (and not vacuum-) driven flow rate of 2.0 in./min are crucial for successful separations by this method.

Experimental Section

Chromatography columns and the flow controller valve were assembled as described in the text. The silica gel used was 40–63 μm (400–230 mesh) silica gel 60 (E. Merck No. 9385).[10] Solvents were distilled prior to use. Thin layer chromatograms (TLC) were run on glass supported silica gel 60 plates (0.25-mm layer, F-254) (E. Merck No. 5765).

Flash Chromatography. General Procedure. First a low viscosity solvent system (e.g., ethyl acetate/30–60 °C petroleum ether)[8] is found which separates the mixture and moves the desired component on analytical TLC to an R_f of 0.35.[9] If several compounds are to be separated which run very close on TLC, adjust the solvent to put the midpoint between the components at R_f = 0.35. If the compounds are widely separated, adjust the R_f of the less mobile component to 0.35. Having chosen the solvent, a column of the appropriate diameter (see text, Table I) is selected and a small plug of glass wool is placed in the tube connecting the stopcock to the column body (A in the diagram above). Two telescoping lengths of glass tubing (6 and 8 mm o.d.) make placement of the glass wool plug easy. Next a smooth ⅛ in. layer of 50–100 mesh sand is added to cover the bottom of the column and dry 40–63 μm silica gel is poured into the column in a single portion to give a depth of 5.5–6 in. With the stopcock open, the column is gently tapped vertically on the bench top to pack the gel. Next a ⅛ in. layer of sand is carefully placed on the flat top of the dry gel bed and the column is clamped for pressure packing and elution. The solvent chosen above is then poured carefully over the sand to fill the column completely. The needle valve (B) of the flow controller is opened all the way and the flow controller is fitted tightly to the top of the column and secured with strong rubber bands. The main air line valve leading to the flow controller is opened slightly and a finger is placed fairly tightly over the bleed port (C). This will cause the pressure above the adsorbent bed to climb rapidly and compress the silica gel as solvent is rapidly forced through the column. It is important to maintain the pressure until *all* the air is expelled and the lower part of the column is cool; otherwise, the column will fragment and should be repacked unless the separation desired is a trivial one. Particular care is necessary with large diameter columns. The pressure is then released and excess eluant is forced out of the column above the adsorbent bed by partially blocking the bleed port (C). The top of the silica gel should not be allowed to run dry. Next the sample is applied by pipette as a 20–25% solution in the eluant to the top of the adsorbent bed and the flow controller is briefly placed on top of the column to push all of the sample into the silica gel.[11] The solvent used to pack the column is ordinarily reused to elute the column. The walls of the column are washed down with a few milliliters of fresh eluant, the washings are pushed into the gel as before, and the column is carefully filled with eluant so as not to disturb the adsorbent bed. The flow controller is finally secured to the column and adjusted to cause the surface of the solvent in the column to fall 2.0 in./min. This seems to be an optimum value of the flow rate for most low viscosity solvents for any column diameter with the 40–63 μm silica gel. Fractions are

collected until all the solvent has been used (see Table I to estimate the amount of solvent and fraction size). It is best not to let the column run dry since further elution is occasionally necessary. Purified components are identified as described in the text by TLC. If the foregoing instructions are followed *exactly*, there is little opportunity for the separation to fail.

Although we generally pack fresh columns for each separation, the expense of large-scale separations makes it advantageous to reuse large diameter columns. Column recycling is effected by first flushing (rate = 2 in./min) the column with approximately 5 in. of the more polar component in the eluant (generally ethyl acetate or acetone) and then with 5 in. of the desired eluant. If the eluant is relatively nonpolar (e.g., ≤10% EtOAc/petroleum ether), it may be more advisable to use a flushing solvent (e.g., 20–50% EtOAc/petroleum ether) which is somewhat less polar than the pure high polarity component.

Registry No.—1, 66417-28-5; **2**, 66417-27-4.

References and Notes

(1) Such units have been described and used extensively by J. M. McCall, R. E. TenBrinkt, and C. H. Lin at the Upjohn Company and A. I. Meyers at Colorado State University.
(2) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(3) This is not a limitation but is merely the scale range which we have used.
(4) This is the total time required for column packing, sample application, and complete elution.
(5) Standard conditions: 5 in. high bed of 40–63 μm silica gel 60 in a 20 mm diameter column packed as described in text, 2.0 in. of solvent flow/min, 200 mg of benzyl alcohol, 25% ethyl acetate/petroleum ether eluant.
(6) These gels are manufactured by E. Merck and are the following grades: <40 μm (silica gel H, No. 7736), 25–40 μm (LiChroPrep Si60, No. 9390), 40–63 μm (silica gel 60, No. 9385), 63–200 μm (silica gel 60, No. 10180).
(7) Slurry packing, incremental dry packing, or single portion dry packing gave identical results with the 40–63 μm gel. Since the last technique was the simplest, it was employed in all our studies.
(8) This is a particularly good general solvent system. For extremely polar compounds, acetone/petroleum ether or acetone/methylene chloride mixtures are often useful. Significantly higher viscosity solvents will require slower optimum resolution flow rates.
(9) If this R_f is given by a solvent having <2% of the polar component, a slightly less polar eluant is desirable. Thus if 1% ethyl acetate/petroleum ether gives a compound an R_f of 0.35 on TLC, the column is run with 0.5% ethyl acetate.
(10) 40–63 μm gel is also used for medium pressure chromatography[1] and is available from MCB in 1 kg ($45/kg) or 25 kg ($16/kg) lots.
(11) If the sample is only partially soluble in the eluant, just enough of the more polar component is added to give complete dissolution. Large quantities of very polar impurities are best removed prior to chromatography so that excessive quantities of solvent or large increases in solvent polarity will be unnecessary for sample application.

Homo-*C*-nucleosides. The Synthesis of Certain 6-Substituted 4-Pyrimidinones[1]

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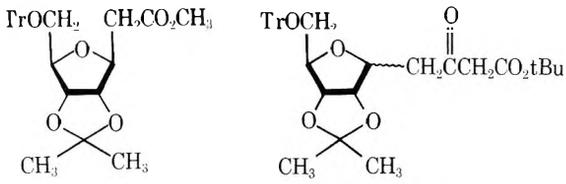
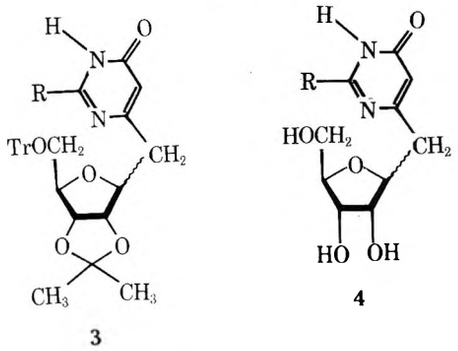
The chemistry of *C*-nucleosides has received considerable attention recently due to the biological activities of naturally occurring compounds such as showdomycin, formycin, and oxazinomycin.[2] Though synthetic methodology has evolved for the preparation of a number of *C*-nucleoside analogues,[2] only one investigation has dealt with the synthesis of homo-*C*-nucleosides,[3] compounds with a methylene unit between a carbon of the nitrogen base and the standard D-ribose moiety. This note describes the facile synthesis of a series of 6-substituted 4-pyrimidinone homo-*C*-nucleosides from the ester **1**, which is available in three steps from D-ribose.[4,5]

Treatment of **1** with lithio-*tert*-butyl acetate[6] in toluene at 0 °C for several hours affords an anomeric mixture (ca. 3:1, β/α) of the β-keto ester **2** in 75% yield. The assignment of β to the major anomer was made on the basis of ^{13}C NMR data. In particular, the isopropylidene methyls of the major anomer



Tr = trityl



a, R = NH_2
b, R = CH_3
c, R = SH
d, R = phenyl
e, R = H

occur at δ 25.66 and 27.54, within the range strongly indicative of a β configuration (25.5 ± 0.2 and 27.5 ± 0.2).[7,8]

It has been shown that the α-anomer of **1** is more stable than the β,[4] and recently a rationalization for this seemingly unusual behavior has been presented.[9] On this basis it seems likely that the α anomer of **2** is also more stable than the β. The conditions involved in the preparation of **2** (low-temperature, aprotic solvent) probably do not allow equilibration, though there is some leakage to the α-anomer. Further support for these postulates is provided by the finding that β-**2** is isomerized readily under basic conditions to an α/β mixture which is predominantly α.

Condensation of **2** with guanidine, acetamidine, thiourea, and benzamidine under basic conditions afforded the protected nucleosides **3a–d** as anomeric mixtures (ca. 3:1, α/β) which were chromatographically inseparable. That the major anomers after condensation are all α is also indicated by the chemical shifts of the isopropylidene methyls. For example, the shifts of the methyls in **3a** are at δ 25.09 and 26.33, clearly in the α range (24.9 ± 0.3 and 26.3 ± 0.2).[7,8] In view of the ready isomerization of β-**2** to a mixture of anomers containing predominantly α-**2**, it seems likely that equilibration is occurring prior to cyclization, and that the anomeric composition of **2** after equilibration dictates the ratio of α- and β-homo-*C*-nucleosides. Desulfurization of **3c** with Raney Nickel in refluxing 95% ethanol provided the hydrogen-substituted compound **3e**. Interestingly, while both urea and formamidine reacted with **2**, neither led to the formation of cyclized material under a variety of conditions. The free nucleosides **4a–e** were obtained by treatment of **3a–e** with either methanolic hydrogen chloride or aqueous trifluoroacetic acid for several hours. These acidic conditions, even over longer periods of time (2 days), caused no change in the α/β ratio of the nucleosides. Chromatographic separation of the free nucleoside anomers was once again not possible. **4e** was also available by desulfurization of **4c**.

The ^{13}C NMR spectra of the free nucleosides contained characteristic signals for the five compounds, and all values are reported in the Experimental Section. Salient ^1H NMR values are the methyl singlet of **4b** at δ 2.28 and the pyrimidine C_2H singlet of **4e** at δ 8.92, as well as the pyrimidine C_5 signal of all five nucleosides in the neighborhood of δ 6.0.

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Thus, homo-*C*-nucleosides are available in only six (**4a–d**) or seven (**4e**) steps from D-ribose in reasonable yields.[10] The β-keto ester **2** is a stable and versatile intermediate which might also serve as a precursor to various other homo-*C*-nucleoside ring systems, as well.

Experimental Section[11]

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. ^{1}H NMR spectra were measured with Varian A60A or EM-360 instruments and ^{13}C NMR spectra with a Bruker WP80; chemical shifts are in parts per million downfield from internal tetramethylsilane or DSS (for D_2O). Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. and Mr. William Rond, The Ohio State University.[12]

Methanol was dried by distillation from magnesium methoxide and toluene by distillation from calcium hydride.

***tert*-Butyl 4-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)-3-oxobutanoate (2).** A solution of 1.86 g (3.82 mmol) of **1** in 10 mL of toluene under nitrogen was cooled to 0–5 °C and 0.93 g (7.64 mmol) of lithio-*tert*-butyl acetate was added in one portion. The solution was stirred several hours and processed by washing several times with water, drying (Na_2SO_4), and evaporation to a light yellow syrup. Column chromatography (silica gel, 2.4 × 40 cm, elution with 4:1 petroleum ether (30–60 °C)–ether) afforded the colorless β-keto ester **2**, 1.46 g (68%), as a thick syrup. Comparable yields (60–75%) have been obtained on runs of up to 20 mmol: IR (neat) 1717, 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.30 and 1.51 (2s, 6, $C(CH_3)_2$), 1.42 and 1.45 (2s, 9, $C(CH_3)_3$, β and α), 2.59–2.94 (m, 2, $CH_2C(O)C$), 3.13–3.72 (m, 4, CH_2OTr and $-C(O)CH_2C(O)-$), 4.02–4.80 (m, 4, C_1H, C_2H, C_3H, C_4H), 7.10–7.60 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.66, 27.54, 27.96, 46.62, 51.06, 64.22, 80.42, 80.90, 82.23, 83.57, 84.53, 86.73, 114.37, 127.04, 127.84, 128.75, 143.83, 166.18, 200.72; mass spectrum calcd *m/e* 572.2773; found 572.2781. Anal. Calcd for $C_{35}H_{40}O_7$: C, 73.40; H, 7.04. Found: C, 73.65; H, 7.25.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxy-2-aminopyrimidine (3a). To a solution of 650 mg (1.14 mmol) of **2** in 12 mL of absolute ethanol was added 120 mg (1.25 mmol) of guanidine hydrochloride and 132 mg (1.25 mmol) of Na_2CO_3, and the mixture was heated at reflux (drying tube) for 12 h. Removal of solvent under reduced pressure followed by dissolution in $CHCl_3$, washing with H_2O, drying, and evaporation afforded an off-white foam, which was purified by column chromatography (silica gel, 2.5 × 20 cm, elution with 97.5–2.5 $CHCl_3$–CH_3OH) to afford 450 mg (73%) of a colorless foam. On standing in a small amount of CH_3OH, the α-anomer (as judged by ^{13}C NMR) crystallized out: mp 236–241 °C dec (begins turning brown at 228 °C); NMR ($CDCl_3$) δ 1.30 and 1.46 (2s, 6, $C(CH_3)_2$), 2.76 (m, 2, CH_2 pyrimidine), 3.21 (m, 2, CH_2OTr), 4.03–4.80 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 5.68, 5.73 (2s, 1, C=CH, α and β), 7.08–7.58 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.09, 26.33, 36.31, 64.69, 80.28, 82.17, 83.47, 87.30, 102.40, 112.49, 127.22, 127.92, 128.68, 143.62, 156.03, 168.55. Anal. Calcd for $C_{32}H_{33}N_3O_5$: C, 71.22; H, 6.16; N, 7.79. Found: C, 71.03; H. 6.16; N, 7.75.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxy-2-methylpyrimidine (3b). A solution containing 1.098 g (1.92 mmol) of **2**, 363 mg (3.84 mmol) of acetamidine hydrochloride, and sodium methoxide (5.76 mmol) in 10 mL of methanol was heated at reflux (drying tube) for 10 h. After evaporation of the solvent under reduced pressure the residue was taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to dryness. Purification was accomplished by column chromatography (silica gel, 2.5 × 18 cm, elution with 97.5–2.5 $CHCl_3$–CH_3OH), yielding 795 mg (77%) of a foam: NMR ($CDCl_3$) δ 1.32 and 1.52 (2s, 6, $C(CH_3)_2$), 2.33 and 2.41 (2s, 3, CH_3C=C, α- and β-anomers), 2.90 (m, 2, CH_2 pyrimidine), 3.23 (m, 2, CH_2OTr), 4.05–4.88 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.29 and 6.37 (2s, 1, C=CH, α- and β-anomers), 7.08–7.58 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.20, 26.38, 38.04, 64.69, 80.01, 82.17, 83.36, 83.52, 87.24, 110.71, 112.44, 127.11, 127.87, 128.68, 143.68, 158.52, 165.85, 167.20. Anal. Calcd for $C_{33}H_{34}N_2O_5$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.70; H, 6.50; N, 5.02.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and β-D-ribofuranosyl)methyl-4-hydroxy-2-thiopyrimidine (3c). A solution containing 1.215 g (2.12 mmol) of **2**, 404 mg of thiourea (5.3 mmol), and sodium methoxide (4.25 mmol) in 15 mL of CH_3OH was heated at reflux (drying tube) for 5 h. After evaporation of the solvent under reduced pressure the residue was taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to dryness. Purification was accomplished by column chromatography (silica gel, 2.5 × 40 cm, elution with 98.5–1.5 $CHCl_3$–CH_3OH) affording 692 mg (59%) of a colorless foam: NMR ($CDCl_3$) δ 1.35 and 1.52 (2s, 6, $C(CH_3)_2$), 2.74 (m, 2, CH_2 pyrimidine), 3.29 (m, 2, CH_2OTr), 4.13–4.83 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 5.78 (s, 1, C=CH), 7.05–7.58 (m, 15, ArH), 10.56 and 11.07 (2 br s, 2, 2 NH); ^{13}C NMR($CDCl_3$) δ 24.76, 26.17, 33.29, 64.74, 79.96, 81.85, 83.20, 84.06, 87.46, 104.56, 112.98, 127.33, 128.03, 128.57, 143.36, 153.71, 161.54, 175.57; mass spectrum calcd *m/e* 556.2032; found 556.2041. Anal. Calcd for $C_{32}H_{32}N_2O_5S$·CH_3OH: C, 67.33; H, 6.16; N, 4.76. Found: C, 67.17; H, 6.32; N, 4.68.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α and -β-D-ribofuranosyl)methyl-4-hydroxy-2-phenylpyrimidine (3d). A solution of **2** (762 mg, 1.36 mmol), benzamidine hydrochloride (277 mg, 1.77 mmol), and sodium ethoxide (3.13 mmol) in 12 mL of absolute ethanol was heated at reflux (drying tube) for 12 h. The reaction mixture was evaporated to dryness, taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to an off-white foam. Purification was accomplished by column chromatography (silica gel, 2.5 × 15 cm, elution with 98–2 $CHCl_3$–CH_3OH), affording 541 mg (68%) of a colorless foam: NMR ($CDCl_3$) δ 1.33 and 1.53 (2s, 6, $C(CH_3)_2$), 2.78–3.50 (m, 4, $2CH_2$), 4.02–5.08 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.38, 6.46 (2s, 1, C=CH, β- and α-anomers), 6.98–7.65 (m, 18, ArH), 7.95–8.38 (m, 2, ortho protons of the 2-phenyl moiety); ^{13}C NMR ($CDCl_3$) δ 25.20, 26.44, 37.99, 65.01, 80.23, 82.28, 83.47, 87.24, 112.38, 127.06, 127.87, 128.63, 131.97, 143.62, 156.47, 165.46, 166.61; mass spectrum calcd *m/e* 600.2624; found 600.2636. Anal. Calcd for $C_{38}H_{36}N_2O_5$·CH_3OH: C, 74.02; H. 6.37; N, 4.43. Found: C, 73.74; H, 6.16; N, 4.20.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxypyrimidine (3e). To a solution of 289 mg (0.52 mmol) of **3c** in 5 mL of 95% ethanol was added 580 mg of Raney Nickel, and the mixture heated at reflux 4 h. Processing and purification was accomplished by filtration through Celite (wash with 95% ethanol), evaporation, and thick layer chromatography (silica gel, two elutions with $CHCl_3$), to afford 196 mg (72%) of a colorless foam. On a 1–2 mmol scale column chromatography (elution with 95–5 $CHCl_3$–CH_3OH) was employed: NMR ($CDCl_3$) δ 1.32 and 1.52 (2s, 6, $C(CH_3)_2$), 2.73–3.46 (m, 4, $2CH_2$), 4.03–4.85 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.41, 6.50 (2s, 1, C_5H of pyrimidine, β- and α-anomers); 7.07–7.60 (m, 15, ArH), 8.09 (s, 1, C_2H of pyrimidine), 13.18 (br s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 25.09, 26.33, 37.93, 64.53, 79.90. 82.06, 82.33, 83.30, 87.19, 112.39, 127.11, 127.87. 128.63, 143.62, 148.05, 164.56, 167.20. Anal. Calcd for $C_{32}H_{32}N_2O_5$·CH_3OH: C, 71.20, H. 6.52, N, 5.03. Found: C, 71.01; H, 6.26; N, 4.99.

General Procedure for the Preparation of 4a–e by Deprotection of 3a–e. A solution of **3a–e** (1 mmol) in 10 mL of 10% methanolic hydrogen chloride was allowed to stand at room temperature for 3 h. Solvent was evaporated and the residue was triturated with ether to remove trityl methyl ether. The residue was taken up in methanol and washed through an Amberlite IR-45 (OH^-) column (1 × 15 cm) with 200 mL of 50% aqueous methanol. Solvent was evaporated and the residue was purified by thick layer chromatography (elution with 1:1 $CHCl_3$–CH_3OH) to afford the free nucleoside as a colorless foam. Deprotection with 9:1 trifluoroacetic acid–H_2O gave comparable results.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-aminopyrimidine (4a): 86%; NMR (Me_2SO-d_6) δ 2.63 (m, 2, CH_2 pyrimidine), 3.17–4.37 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH), 5.53 (s, 1, C=CH), 6.77 (br s, 2, NH_2); ^{13}C NMR (Me_2SO-d_6) δ 37.67 (CH_2 pyrimidine), 61.66 (CH_2OH), 71.76, 72.05, 78.55, 81.81 (C_1, C_2, C_3, C_4 of carbohydrate), 101.03 (pyrimidine C_5), 155.41 (pyrimidine C_6), 163.27 (pyrimidine C_4), 166.57 (pyrimidine C_2). Anal. Calcd for $C_{10}H_{15}N_3O_5$·0.5CH_3OH: C, 46.15; H. 6.27; N, 15.38. Found: C, 46.33; H, 6.06, N, 15.67.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-methylpyrimidine (4b): 56%; NMR (Me_2SO-d_6) δ 2.28 (s, 3, CH_3), 2.73 (m, 2, CH_2 pyrimidine), 3.35–4.42 (m. 6, C_1H, C_2H, C_3H, C_4H, CH_2OH), 6.06 (s, 1, C=CH); ^{13}C NMR (Me_2SO-d_6) δ 21.02 (CH_3), 37.58 (CH_2 pyrimidine), 61.65 (CH_2OH), 71.76, 72.05, 78.26, 81.90 (C_1, C_2, C_3, C_4 of carbohydrate), 110.30 (pyrimidine C_5), 158.42, 162.54, 164.92 (pyrimidine C_2, C_4, C_6). Anal. Calcd for $C_{11}H_{16}N_2O_5$·0.5CH_3OH: C, 50.73; H, 6.66; N, 10.29. Found: C, 50.57; H. 6.34; N, 10.49.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-thiopyrimidine (4c): 77%; NMR (Me_2SO-d_6) δ 2.65 (m, 2, CH_2 pyrimidine), 3.35–4.35 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH), 5.75 (s, 1, C=CH); ^{13}C NMR (Me_2SO-d_6) 32.92 (CH_2 pyrimidine), 61.41 (CH_2OH), 71.71, 77.73, 82.05 (C_1, C_2, C_3, C_4 of carbohydrate), 103.94 (pyrimidine C_5), 154.97 (pyrimidine C_6, 161.09 (pyrimidine C_4), 175.89 (pyrimidine C_2). Anal. Calcd for $C_{10}H_{14}N_2O_5S$·CH_3OH: C, 43.13; H, 5.92. Found: C, 43.27; H, 5.93.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-

phenylpyrimidine (4d): 86%; (Me_2SO-d_6) δ 2.87 (m, 2, CH_2 pyrimidine), 3.30–4.57 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH), 5.85 (br s, OH), 6.29 (s, 1, C=CH), 7.58 (m, 3, *m*- and *p*-ArH), 8.17 (m, 2, *o*-ArH); ^{13}C NMR (Me_2SO-d_6) δ 37.77 (CH_2 pyrimidine), 61.66 (CH_2OH), 71.80, 72.05, 78.50, 81.95 (C_1, C_2, C_3, C_4 of carbohydrate), 110.40 (pyrimidine C_5), 127.68, 128.51, 131.32, 133.17 (aromatic), 157.30 (pyrimidine C_6), 164.29, 165.36 (pyrimidine C_2, C_4). Anal. Calcd for $C_{16}H_{18}N_2O_5 \cdot CH_3OH$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.70; H. 6.25; N, 7.93.

6-*C*-(α and β-D-Ribofuranosyl)methyl-4-hydroxypyrimidine (4e): 82%; NMR (D_2O) δ 2.87 (m, 2, CH_2 pyrimidine), 3.30–4.57 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH of carbohydrate), 6.51 (s, 1, pyrimidine C_5H), 8.92 (s, 1, pyrimidine C_2H); ^{13}C NMR (Me_2SO-d_6) δ 61.66 (CH_2OH), 71.73, 72.05, 78.24, 81.95 (C_1, C_2, C_3, C_4 of carbohydrate), 113.22 (pyrimidine C_5), 149.46 (pyrimidine C_2), 161.89, 164.95 (pyrimidine C_4, C_6), CH_2 pyrimidine obscured by Me_2SO peaks. Anal. Calcd for $C_{10}H_{14}N_2O_5 \cdot 0.8CH_3OH$: C, 48.43; H. 6.47; N, 10.46. Found: C, 48.08; H. 6.19; N, 10.62.

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Registry No.—**1,** 56752-57-9; α-**2,** 66358-76-7; β-**2,** 66358-77-8; α-**3a,** 66358-78-9; β-**3a,** 66358-79-0; α-**3b,** 66358-80-3; β-**3b,** 66358-81-4; α-**3c,** 66358-82-5; β-**3c,** 66358-83-6; α-**3d,** 66358-84-7; β-**3d,** 66358-85-8; α-**3e,** 66358-86-9; β-**3e,** 66358-87-0; α-**4a,** 66358-88-1; β-**4a,** 66358-89-2; α-**4b,** 66416-41-9; β-**4b,** 66358-90-5; α-**4c,** 66358-91-6; β-**4c,** 66358-92-7; α-**4d,** 66358-93-8; β-**4d,** 66358-94-9; α-**4e,** 66358-95-0; β-**4e,** 66358-96-1; guanidine hydrochloride, 50-01-1; acetamidine hydrochloride, 124-42-5; thiourea, 62-56-6; benzamidine hydrochloride, 1670-14-0.

References and Notes

(1) Dedicated to Professor Melvin S. Newman on the occasion of his 70th birthday.
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(7) See ref 4 for the first use of the shift positions in the ^{13}C NMR to assign anomeric configuration in *C*-nucleoside precursors.
(8) We have found that in the vast majority of cases $\Delta\delta$ for the β anomer is 1.89 ± 0.1 and for the α anomer 1.24 ± 0.1. Compound **3c** is slightly outisde this limit.
(9) H. Ohrui and S. Emoto, *J. Org. Chem.*, **42**, 1951–1957 (1977).
(10) Preliminary antibacterial screening on several of these compounds at the Lilly Research Laboratories has shown no significant activity.
(11) Spectral data are for the major anomer unless otherwise indicated for specific resonances.
(12) In all cases where analyses include methanol, the methyl protons were observed in the ^1H NMR spectrum.

Substitution Reactions of 17α-Vinyl-17β-trifluoroacetoxy Steroids

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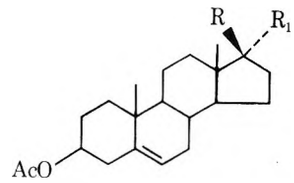
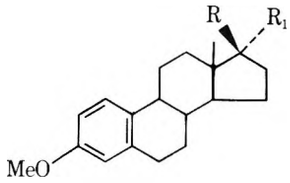
In continuation of our studies[1] on the trifluoroacetoxy group as a useful intermediate in the nucleophilic substitution of those steroid alcohols whose tosylates are difficult to obtain or isolate we became interested in the behavior of the 17α-vinyl-17β-trifluoroacetoxy derivatives **1** and **2,** prepared from the corresponding alcohols **1a**[2] and **2a**[3] with trifluoroacetic anhydride–pyridine at 0 °C.

Methanolysis of **1** in the presence of sodium acetate afforded 17α-methoxypregna-5,20-dien-3β-yl acetate (**1b**), (*E*)-21-methoxypregna-5,17(20)-dien-3β-yl acetate (**1c**), starting alcohol **1a,** and (*E*)-pregna-5,17(20)-dien-3β,21-diol 3-acetate (**1d**).[4]



1, R = $OCOCF_3$; R_1 = CH=CH_2
1a, R = OH; R_1 = CH=CH_2
b, R = CH=CH_2; R_1 = OMe
c, R = R_1 = =$CHCH_2OMe$[a]
d, R = R_1 = =$CHCH_2OH$[a]
e, R = R_1 = =$CHCH_2N_3$[a]
f, R = R_1 = =$CHCH_2OCOCF_3$[a]
g, R = R_1 = =$CHCH_2Cl$[a]
h, R = R_1 = =$CHCH_2OAc$[a]



2, R = $OCOCF_3$; R_1 = CH=CH_2
2a, R = OH; R_1 = CH=CH_2
b, R = R_1 = =$CHCH_2N_3$[a]
c, R = R_1 = =$CHCH_2Cl$[a]

[a] *E* isomers.

The structures **1b, 1c,** and **1d** were inferred from their analytical and spectral (IR and ^1H-NMR) data.

The methoxy group in **1b** was assigned the 17α configuration on the basis of the upfield position of the 13-Me group compared with that of the 17β derivatives **1, 1a,** and **2.**[1a]

Evidence for the trans stereochemistry at the 17(20) double bond in **1c** and **1d** was likewise obtained by comparison of their 13-Me shifts with those of compounds of known stereochemistry.[5]

1d was furthermore acetylated to give the known diacetate **1h.**[3]

The product pattern was nearly what one would expect from competing S_N1 and $B_{Ac}2$ mechanisms,[1a] the absence of a 17β-methoxy derivative being expected because of steric reasons.[1a]

The presence in high yield of the rearranged alcohol **1d** required nevertheless further investigation.

Isomerization of the initially formed alcohol **1a** appeared untenable since conversions of this type are acid catalyzed.[3]

1d could have instead resulted, via an acyl–oxygen cleavage, from the corresponding trifluoroacetate **1f,** in turn obtained by partial isomerization of **1** in the reaction medium.

That **1f** is probably the precursor of **1d** was supported by the fact that buffered methanolysis of **1f** in the same conditions as used for **1** afforded very quickly **1d** exclusively.

This fast consumption of **1f** joined to its probable slow formation (also see later) should account for our inability to detect it in the course of the methanolysis of **1.**

Bimolecular substitutions of **1** and **2** by azide ion in hexamethylphosphotriamide (HMPT) to give the 21-azido derivatives **1e** and **2b** proceeded in high yield (>70%).

1e and **2b** were assigned the trans stereochemistry on the same basis as discussed before.

As to the mechanism, these azidolyses cannot be regarded as pure S_N2' processes, since **1** has been found to rearrange partially into **1f** in HMPT and this latter was shown to afford quantitatively **1e** in the presence of NaN_3.

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From a synthetic point of view methanolysis of **1** (and likely similar unimolecular solvolyses) appears to be of limited usefulness. Solvolysis of **1** and **2** in aprotic solvents in the presence of strong nucleophiles should conversely represent a good alternative to the displacement of analogous 21-chloro derivatives **1g**[2] and **2c**[5] for the introduction of substituents at C-21.

Experimental Section[6]

17α-Pregna-5,20-dien-3β,17-diol 3-Acetate 17-Trifluoroacetate (1). A solution of 17α-pregna-5,20-dien-3β,17-diol 3-acetate (**1a**)[2] (0.36 g, 1 mmol) in pyridine (1.7 mL) was treated with trifluoroacetic anhydride (0.7 mL) at 0 °C for 15 min. Then cold 1 N HCl (11.7 mL) was added and the mixture was extracted with ether. The ether layers were washed to neutrality with cold water, dried (Na_2SO_4), and evaporated. The residue (0.45 g) was crystallized from *n*-hexane (0.33 g): mp 118–119 °C; $[\alpha]_D$ −39°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.95 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.13 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.33 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.37 (1 H, m, C-6H), 5.91 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H).[7] Anal. Calcd for $C_{25}H_{33}F_3O_4$ (454.5): C, 66.06; H, 7.32; F, 12.54. Found: C, 66.06; H, 7.32; F, 12.52.

Solvolysis of 1 in Methanol in the Presence of Sodium Acetate. A stirred solution of **1** (0.30 g, 0.66 mmol) and sodium acetate (0.11 g, 1.32 mmol) in 8 mL of methanol was heated at 60 °C for 4 h.[8] Methanol was then evaporated and the product was isolated with ether. The ethereal solution was washed twice with water and then dried (Na_2SO_4). The residue (0.25 g) was chromatographed on alumina (1.25 g). Elution with *n*-hexane–benzene (1:1) gave olefins (15 mg, 6%), followed by **17 α-methoxypregna-5,20-dien-3β-yl acetate (1b,** 23 mg, 9%): mp 137–138 °C (from methanol); $[\alpha]_D$ −83°; ^1H NMR δ 0.59 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 3.05 (3 H, s, 17α-OMe), 4.6 (1 H, m, 3α-H), 5.10 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.25 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.38 (1 H, m, C-6 H), 5.69 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H).[7] Anal. Calcd for $C_{24}H_{36}O_3$ (372.5): C, 77.37; H, 9.74. Found: C, 77.31; H, 9.77.

Elution with benzene gave first **(*E*)-21-methoxypregna-5,17(20)-dien-3β-yl acetate** (1c, 53 mg, 21%): mp 87.5–88.5 °C (from methanol); $[\alpha]_D$ −63°; ^1H NMR δ 0.77 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 3.30 (3 H, s, 21-OMe), 3.90 (2H, d, *J* = 7 Hz, CH_2OMe), 4.6 (1 H, m, 3α-H), 5.21 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6 H).[7] Anal. Calcd for $C_{24}H_{36}O_3$ (372.5): C, 77.37; H, 9.74. Found: C, 77.05; H, 9.75.

A second eluate with benzene gave the alcohol **1a** (22 mg, 9%).

Finally elution with benzene–ether (7:3) gave **(*E*)-pregna-5,17(20)-dien-3β,21-diol 3-acetate (1d,** 122 mg, 49%): mp 177–178 °C (from diisopropyl ether); $[\alpha]_D$ −61°; ^1H NMR δ 0.77 (3 H, s, 13-Me), 1.03 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.12 (2 H, d, *J* = 7 Hz, CH_2OH), 4.6 (1 H, m, 3α-H), 5.28 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.38 (1 H, m, C-6 H).[7] Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 76.80; H, 9.55.

(*E*)-Pregna-5,17(20)-dien-3β,21-diol 3-Acetate 21-Trifluoroacetate (1f). This was prepared in the same manner as **1** from 21-alcohol **1d** and crystallized from *n*-hexane: mp 99–101 °C; $[\alpha]_D$ −49°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.78 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 4.82 (2 H, d, *J* = 7 Hz, CH_2OCOCF_3), 5.27 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6H).[7] Anal. Calcd for $C_{25}H_{33}F_3O_4$ (454.5): C, 66.06; H, 7.32; F, 12.54. Found: C, 66.13; H, 7.48; F, 12.54.

Solvolysis of 21-trifluoroacetate 1f in methanol in the presence of sodium acetate under the same conditions as for **1** resulted, after 15 min,[8] in the formation of the 21-alcohol **1d** exclusively.

Solvolysis of 17β-Trifluoroacetate 1 in HMPT in the Presence of NaN_3. **1** (0.23 g, 0.5 mmol) and NaN_3 (0.32 g, 5 mmol) in 5 mL of HMPT were stirred at 60 °C for 5 h.[8] The mixture was poured into water and extracted with ether. The extract was washed with water to neutrality and dried (Na_2SO_4). The residue (0.19 g) was directly crystallized from *n*-hexane to afford 0.14 g (73%) of **(*E*)-21-azido-pregna-5,17(20)-dien-3β-yl acetate (1e):** mp 105–106 °C; $[\alpha]_D$ −56°; IR (N_3) 2100 cm^{-1}; ^1H NMR δ 0.78 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 4.82 (2 H, d, CH_2N_3), 5.27 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6H).[7] Anal. Calcd for $C_{23}H_{33}N_3O_2$ (382.5): C, 72.02; H, 8.67; N, 10.96. Found: C, 72.03; H, 8.76; N, 10.81.

The only other components found in the mother liquors were a relatively nonpolar substance (7%)[4] and alcohol **1d** in traces.

In the same manner as above solvolysis of **1f** was carried out in HMPT + NaN_3 to give **1e** in 1 h[8] in 100% yield.

When **1** was heated in HMPT at 60 °C partial isomerization into **1f** occurred. NMR analysis showed a **1**:**1f** = 85:15 ratio after 1 h. The ratio went down to a 66:34 value in 3 h.

3-Methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-yl Trifluoroacetate (2). This was prepared in the same manner as **1** from 3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (**2a**) and crystallized from *n*-hexane: mp 124 °C; $[\alpha]_D$ +72°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.98 (3 H, s, 13-Me), 3.75 (3 H, s, 3-OMe), 5.17 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21H), 5.37 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.97 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H), 6.62–7.23 ppm (3 H, aromatic protons).[7] Anal. Calcd for $C_{23}H_{27}F_3O_3$ (408.5): C, 67.63; H, 6.66; F, 13.95. Found: C, 68.27; H, 6.82; F, 13.96.

Solvolysis of 2 in HMPT in the presence of NaN_3 in the same conditions as for **1** gave 0.17 g of a residue (from 0.20 g of **2**) which was chromatographed on PLC [benzene–*n*-hexane (1:2) as eluant] to afford 0.14 g (82%) of **(*E*)-3-methoxy-21-azido-19-norpregna-1,3,5(10),17(20)-tetraene (2b)** as an oil, pure by NMR analysis: $[\alpha]_D$ +51° (*c* 4.0); IR (N_3) 2100 cm^{-1}; ^1H NMR δ 0.81 (3 H, s, 13-Me), 3.73 (2 H, d, *J* = 7 Hz, CH_2N_3), 3.74 (3 H, s, 3-OMe), 5.23 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 6.62–7.27 (3 H, aromatic protons).[7] Anal. Calcd for $C_{21}H_{27}N_3O$ (337.5): C, 74.74; H, 8.07; N, 12.45. Found: C, 74.58; H, 8.06; N, 12.27.

Registry No.—**1**, 65733-41-7; **1a**, 32782-36-8; **1b**, 65733-42-8; **1c**, 65733-43-9; **1d**, 65733-44-0; **1e**, 65733-45-1; **1f**, 65733-46-2; **2**, 65760-05-6; **2a**, 6885-48-9; **2b**, 65733-47-3.

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(7) A convenient illustration of the features of systems of the type >CCH═CH_2 and >C═$CHCH_2X$ is found in: N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy to Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 85 and 112.
(8) The disappearance of starting material was monitored by TLC.

Photochemical Reduction and Decarboxylation of 2-Phenylquinoline-4-carboxylic Acids

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Though a variety of 2-phenylquinoline-4-carboxylic acids (cinchophens) and their derivatives have medicinal value,[2] some members of the family have been observed by Rothe[3] to cause phototoxicity in mice. We have previously found[5] that the phototoxicity of similar quinolinemethanol antimalarial compounds correlates with a surprisingly efficient photochemical fragmentation process. We have now studied five of the cinchophens and have discovered that, like the quinolinemethanols, these compounds also show unexpected photochemical reactivity.

Acids **1a–e** were prepared via Doebner condensations of the suitably substituted aniline and aldehyde. Irradiation led to

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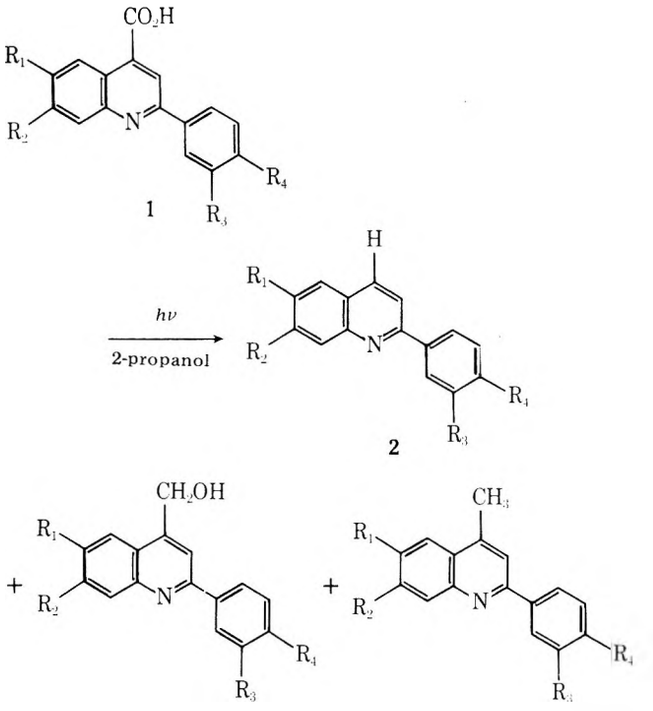
Table I. Isolated Products from Cinchophen Photolyses

compd no.	registry no.	isolated yield, % 2	registry no.	3	registry no.	4	registry no.
1a	19021-20-6	93	61576-11-2	1[a]	61576-10-1	6	66324-17-2
1b	19209-49-5	71	66373-83-9	*b*		5	66324-18-3
1c	20843-19-0	51	66324-15-0	*b*		4	66324-19-4
1d	32795-58-7	66	4789-73-5	2	66324-16-1	*b*	
1e	60538-98-9	86	27356-46-3	*b*		*b*	

[a] Observed only at low conversion. [b] Not detected; estimated yield <1%.



a, $R_1 = R_4 = CH_3O$; $R_2 = Cl$; $R_3 = H$
b, $R_1 = CH_3O$; $R_2 = H$; $R_3 = R_4 = Cl$
c, $R_1 = R_4 = H$; $R_2 = R_4 = F$
d, $R_1 = CH_3O$; $R_2 = R_3 = R_4 = H$
e, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$

photochemical decarboxylation and photoreduction. In all cases the decarboxylation pathway predominated, leading to **2** as the major product. Concurrently, about 5% of **3** or **4** was formed. Generally the products were isolated by silica gel chromatography; Table I summarizes the results obtained from photolysis of each compound.

Identification of products was based upon spectral analysis and independent synthesis. In each case protio compound **2** could be obtained by a thermal decarboxylation of the corresponding acid (**1**). The methanol derivates, **3**, were obtained by reduction of the methyl esters of **1a–e** with lithium aluminum hydride. The methyl compounds, **4**, were prepared by photochemical reduction of alcohol **3**[6] or by hydrogenolysis of the α-chloromethyl compound.

Both the photoreduction and decarboxylation of **1** were surprising, since there are few reports of such photochemical transformations of analogous compounds. The photochemical decarboxylation of arylcarboxylic acids is rare in solution, for reasons which are not entirely clear. Several reports[7] suggest that the preferred pathway of photochemical decarboxylation is via a homolytic fission to produce a radical intermediate. Such a fission would be expected to be more difficult with the carboxyl group directly attached to an aromatic ring, and a slower reaction would not be surprising. Evidence for this argument is found in Takeuchi's observation[8] that the photochemical decarboxylation of nicotinic acid proceeds preferentially from the anionic (ionized) form of the acid. Similarly, Cantrell[9] and Azuma[10] report the reluctance of benzoic acid and monosubstituted pyridine carboxylic acids, respectively, to photochemically decarboxylate in solution. In contrast to the behavior of nicotinic acid,[8] the decarboxylation of **1** does not proceed through an ionic mechanism, since photolysis of **1a** in basic solution retarded the rate of reaction about 50-fold. Further, photolysis in $(CH_3)_2CDOH$ led to incorporation of deuterium in the 4 position of the protio product, suggesting that a hydrogen atom is abstracted in one step of the mechanism, rather than a proton. Whether the reaction proceeds by a direct α cleavage or by an initial reduction of the quinoline ring cannot be determined at this point, however.

The formation of the minor product, **3** or **4**, was most surprising, since it is clearly formed by an unusual pathway. The intermediacy of alcohol **3** in the formation of **4** is probable, since irradiation of **3** under identical conditions leads almost exclusively to formation of the methyl compound. Further, the proportion of **3** is dependent upon extent of photolysis, ordinarily being totally absent at high conversions.

$$\mathbf{1} \xrightarrow[?]{h\nu} \mathbf{3} \xrightarrow{h\nu} \mathbf{4}$$

We have not yet determined whether the conversion of **1** to **3** proceeds by a direct photochemical reduction or by a "chemical sensitization" pathway in which a free radical produced from a different reaction transfers a hydrogen atom to *ground* state **1**.

The conversion of **1a** to **2a** and **4a** could be sensitized with both xanthone and Michler's ketone, and the conversion of **1b** to **2b** and **4b** was successfully sensitized with Michler's ketone, suggesting that the reactive excited state for the cinchophens is the triplet. Although the presence of cyclohexadiene did not affect the reaction of **1a**, the reaction was totally quenched by photolysis in the presence of oxygen, consistent with the assignment of the triplet as the reactive excited state. The proportion of products was independent of the presence of sensitizer or quencher.

We are continuing to investigate the mechanism and generality of the photochemical reactions of quinolinecarboxylic acids.

Experimental Section[11]

Preparation of the Cinchophens (1a–e). All cinchophens were prepared via a Doebner condensation of suitably substituted anilines and benzaldehydes with pyruvic acid.[12]

Irradiation Procedure. Irradiation of 1.0 g (2.9 mmol) of **1a** in 500 mL of 2-propanol for 2 h with a Hanovia 450 W mercury lamp, using a vycor filter, and purging with nitrogen throughout the photolysis was a typical reaction. The photolysate was concentrated in vacuo and separated by extraction into 0.23 g of an acidic fraction (unreacted **1a**) and 0.67 g of a neutral fraction (a mixture of **2a** and **4a**). The photoproducts were isolated by column chromatography of the neutral fraction using silica gel as an adsorbent and eluting with benzene. The results of this isolation procedure are summarized in Table I. The identity of the photoproducts was confirmed by comparison of their

spectral properties and TLC behavior with those of authentic samples prepared as described below.

Thermal Decarboxylation of the Cinchophens. Preparation of Protio Compounds 2a–e. Typically, a 1.0-g sample (2.9 mmol) of **1a** was melted by placing a test tube containing the sample blanketed with nitrogen into a Wood's metal bath at 275 °C for 4 min. Chromatography of the reaction product (silica gel, benzene eluent) gave 0.25 g (29%) of **2a** as the only mobile spot on TLC with benzene as an eluent. Recrystallized (benzene) constant-melting samples gave: **2a,** mp 189–190 °C; **2b,** mp 152–153 °C; **2c,** mp 95–97 °C; **2d,** mp 129–130 °C;[13] **2e,** mp 67 °C.[14]

Preparation of Alcohols 3a–d. Typically, 2.1 g (5.9 mmol) of the methyl ester of acid **1a** was treated with 0.250 g (6.6 mmol) of lithium aluminum hydride in ether. The usual workup gave 1.56 g (80%) of alcohol **3a,** mp 203–205 °C. Similarly, reduction of the methyl ester of **1b** gave **3b,** mp 188–189 °C, reduction of the methyl ester of **1c** gave **3c,** mp 195–196.5 °C, and **1d** led to **3d,** mp 138.5–139.5 °C.

Preparation of the 4-Methyl Derivatives 4a–c. Procedure A: A solution of 0.500 g (1.85 mmol) of alcohol **3c** in 10 mL of chloroform was treated with 0.500 g (2.40 mmol) of phosphorus pentachloride for 24 h. The crude α-chloro compound was subjected to hydrogenolysis using 50 mg of platinum oxide as a catalyst, ethanol solvent, and hydrogen at 45 psi for 1 h. Chromatography of the isolated product (1:1 hexane–benzene, silica gel) gave 0.180 g (38%) of **4c,** mp 95–97 °C. Procedure B: The direct photolysis of alcohols **3a** and **3b** in 2-propanol under nitrogen using a Hanovia 450 W mercury lamp and a Pyrex filter gave respectively **4a,** mp 148–150 °C, and **4b,** mp 130–131 °C. Characteristically, these 4-methyl compounds showed an NMR absorption at δ 2.6–2.7 as a singlet integrating for three protons.

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Registry No.—**3b,** 66324-20-7; **3c,** 66324-21-8.

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Convenient New Procedures for the Synthesis of Ethoxythiocarbonyl Derivatives of Amino Acids[1a]

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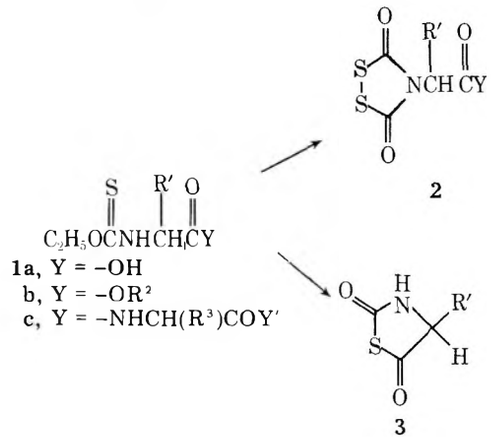
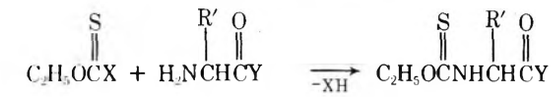
Ethoxythiocarbonyl (Etc) derivatives of amino acids **1a** and their esters **1b** are synthetic precursors to the thiol-labile dithiasuccinoyl (Dts) N^{α}-amino protecting group[2] recently developed for peptide synthesis (**2** in Scheme I). They are also intermediates in the preparation of *N*-thiocarboxy anhydrides **3** of α-amino acids (1,3-thiazolidine-2,5-diones),[3a,b] which were reported to have certain advantages for peptide synthesis[4,5] by comparison to their oxygen analogues, *N*-carboxy anhydrides. Etc derivatives **1a** and **1c** have also been explored for use as reversible amino protecting groups[6] and in a scheme for stepwise degradation of peptides,[7,8] but these applications appear to be of limited scope.

Scheme I. Synthetic Applications of Ethoxythiocarbonyl (Etc) Amino Acids and Derivatives



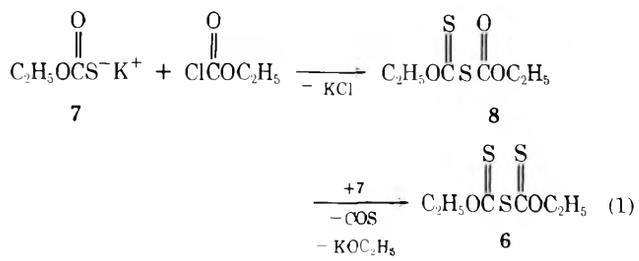
Scheme II. Synthesis of Ethoxythiocarbonyl (Etc) Derivatives of Amino Acids



4, X = –Cl
5, X = –SCH$_3$
6, X = –SCSOC$_2$H$_5$
10, X = –SCH$_2$CO$_2$H

Etc derivatives of amino acids can in principle be prepared with one of the following known reagents: ethoxythiocarbonyl chloride (**4**),[9–11] *O*-ethyl *S*-methyl dithiocarbonate (**5**),[12,13] or bis(ethoxythiocarbonyl) sulfide (**6**)[14–17] (Scheme II). Compound **4** is difficult to prepare and handle.[18] Compound **5,** while allowing formation of Etc derivatives in high yields under alkaline conditions,[4,7,8,19] is unattractive due to the stench of the methanethiol evolved in the reaction. Compound **6** does not have the disadvantages of compounds **4** and **5.** We found that it is easy to prepare and that it reacts rapidly with amino acids in aqueous solutions at pH 8–10 to give the desired derivatives in nearly quantitative yields after a straightforward workup. Progress of the reaction can be followed titrimetrically (an equivalent of base is consumed) or spectrophotometrically (Etc derivatives of amino acids have λ_{max} 245 nm with ϵ 1.3–1.5 × 10^4).

Compound **6** was originally isolated as a by-product from the synthesis of diethyl thionothiodiformate (**8**) on reaction of equimolar amounts of potassium ethyl xanthate (**7**) and ethyl chloroformate (eq 1).[14,20] We found that compound **6**



(1)

can be easily obtained as the main product in place of compound **8** when the molar ratio of ethyl chloroformate to ethyl

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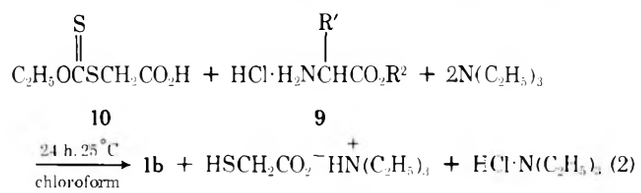
xanthate is decreased to 0.5. The method of preparation reported here is substantially more straightforward than others given in the literature.

Compound **6**, mp 52–53 °C, is completely stable on storage under ambient conditions over a period of years. It is relatively resistant to hydrolysis at pH 10 (estimated half-life 4.5 h). By contrast, the oxa analogue of compound **6**, diethyl pyrocarbonate, has a half-life of 18 min at pH 10.[21] Compound **6** may prove to have comparable utility to diethyl pyrocarbonate[21-24] as a reagent for chemical modification of proteins, and it has the added advantage that the resulting Etc derivatives may be characterized by ultraviolet spectrophotometry.

We also found a general new procedure to prepare pure Etc–amino acid esters **1b** in essentially quantitative yields. Amino acid ester hydrochlorides **9** were reacted with a slight excess of *O*-ethyl *S*-carboxymethyl dithiocarbonate (**10**)[20] in the presence of 2 equiv of triethylamine (eq 2). The reactions



were conducted in homogeneous chloroform solution (yields were somewhat lower in heterogeneous ether solution) at room temperature for 1 day. A standard aqueous acid–base workup isolated the desired Etc–amino acid ester **1b** in the organic phase.

Reagent **10** has often been applied previously[20,25-29] to the preparation of Etc derivatives of primary and secondary aliphatic or aryl amines in moderate to good yields. The xanthate ester has generally[25,27] been generated in situ from sodium or potassium ethyl xanthate and sodium chloroacetate, and the reactions with amines have been carried out in aqueous alkaline solutions. The use of crystalline **10**,[20,28] mp 58–59 °C, as well as the anhydrous reaction conditions reported here, offers several advantages. Among the possible side reactions which appear to be avoided are saponification (under aqueous conditions) of the ester moieties of starting **9** and formation of bis(carboxymethyl) trithiocarbonate[26,29] from further reaction of released mercaptoacetate with the Etc group.

Experimental Section

Melting points were determined in glass capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared absorption spectra were obtained on a Perkin-Elmer 237 B grating spectrophotometer, proton nuclear magnetic resonance spectra on a Varian Model T-60, and ultraviolet absorption spectra on a Cary Model 14 PM recording spectrophotometer. Elemental analyses were performed by Mr. S. T. Bella.

Bis(ethoxythiocarbonyl) Sulfide (Ethylxanthic Anhydride, 6). Potassium hydroxide (85%; 84.2 g, 1.27 mol) was dissolved in 330 mL of absolute ethanol, and 80 mL of carbon disulfide (1.33 mol) was added dropwise. The reaction mixture started boiling spontaneously, and a considerable amount of orange potassium ethyl xanthate crystallized out of solution. All of the crystals were redissolved again upon addition of 220 mL of water. Ethyl chloroformate (57 mL, 0.6 mol) was added, and a yellow oily lower phase immediately separated. Small crystals soon formed, which grew dramatically overnight. These were collected (100 g, crude yield 79%, but gave considerable ash upon combustion) and recrystallized from 800 mL of hot (60 °C) ethanol/water (3:1) to give 72 g (57% overall) of pale yellow needles, mp 52–53 °C (lit.[15] mp 52 °C, lit.[14] mp 55 °C after repeated recrystallizations from absolute ethanol): IR (KBr) 2970 (w), 1390 (w), 1365 (m), 1290 (s), 1240 (w, sh), 1095 (m), 1000 (s), 980 (s), 840 (w) cm^{-1}; NMR ($CDCl_3$) δ 4.70 (q, J = 7 Hz, 2 H, CH_2), 1.48 (t, J = 7 Hz, 3 H, CH_3); UV (ethanol) λ_{max} 302 nm (ϵ 1.8×10^4) and 249 nm (ϵ 6.7×10^3).

Anal. Calcd for $C_6H_{10}O_2S_3$, mol wt 210.34: C, 34.26; H, 4.79. Found: C, 34.38; H, 4.88.

Diethyl Thionothiodiformate (8). Ethyl chloroformate (19 mL, 0.2 mol) was slowly added to a solution of potassium ethyl xanthate (32 g, 0.2 mol) in 50 mL of water, in an exothermic reaction. After cooling to room temperature, the product oil was extracted into ether and dried over sodium sulfate. The title compound was obtained (20 g, 52%) after vacuum distillation under nitrogen, bp 69–75 °C (0.4 mm) [lit.[20] bp 133 °C (18 mm), lit.[30] bp 84–94 °C (1 mm)]: IR (neat) 2980 (w), 1785 (w), 1755 (s), 1720 (sh), 1440 (w), 1365 (w), 1260 (s), 1135 (s), 1100 (s), 1050 (s), 840 (w), 690 (s); UV (ethanol) λ_{max} 273 nm (ϵ 9.4×10^3).

A brown residue from the distillation step spontaneously solidified. After recrystallization from ethanol/water (3:1), this substance was shown to be identical with **6** by mixture melting point and IR.

The stability of reagent **8** in aqueous solutions was evaluated by UV spectroscopy. In pH 8.1, 0.1 M $NaHCO_3$ buffer, hydrolysis proceeded with a half-time of 9 min. The product was sodium ethyl xanthate (101%): λ_{max} 303 nm (ϵ 1.15×10^4) and 227 nm (ϵ 6.13×10^3).

***O*-Ethyl *S*-Carboxymethyl Dithiocarbonate (10).** Solid potassium ethyl xanthate (690 g, nominally 4.3 mol, practical grade pellets) was added to a chilled solution of sodium chloroacetate (500 g, nominally 4.3 mol, practical grade) in 2.2 L of water. After 3 h at room temperature, the reaction mixture was acidified with concentrated sulfuric acid (110 mL, 3.9 mol), and the yellowish-brown lower phase was taken. After standing for 2 weeks in the presence of petroleum ether (bp 30–60 °C), a substantial mass (220 g, 1.2 mol) of large light-brown crystals, mp 53–54 °C, suddenly formed. Further crystalline material (total initial isolated yield 57%) was obtained by extraction of the mother liquor into aqueous sodium bicarbonate and subsequent reacidification.

All material was effectively recrystallized (average yield 60%) by dissolving in chloroform (1 g/2.5 mL) and layering on several volumes of petroleum ether. Crystals initially formed at the interphase as the petroleum ether diffused; after a while, the phases were stirred up. Crystals were collected and washed liberally with petroleum ether; the color was completely removed by washing with a small amount of chloroform/petroleum ether (1:3). Various batches were white needles, long colorless rods, or beautiful large colorless plates, mp 58–59 °C (lit.[20] mp 58 °C, lit.[28] mp 57–58 °C), pure by thin layer chromatography in chloroform/acetic acid (19:1), R_f 0.59: NMR ($CDCl_3$) δ 11.87 (s, 1 H, COOH), 4.68 (q, J = 7 Hz, 2 H, Etc CH_2), 4.00 (s, 2 H, SCH_2), 1.43 (t, J = 7 Hz, 3 H, Etc CH_3); UV (ethanol) λ_{max} 278 nm (ϵ 1.1×10^4) and 221 nm (ϵ 6.5×10^3).

Anal. Calcd for $C_5H_8S_2O_3$, mol wt 180.25: C, 33.32: H, 4.47. Found (corrected for 0.2% ash): C, 33.37; H, 4.45.

General Procedure for Preparation of Ethoxythiocarbonyl (Etc)-L-amino Acids (1a). An amino acid (50 mmol) and bis(ethoxythiocarbonyl) sulfide (**6**) (12 g, 57 mmol) were suspended in 160 mL of water and 210 mL of ethanol. A total of 110 mL of 1 N sodium hydroxide was added at room temperature: half of it at once and the remainder over 10 min. With the last few drops of base, the reaction mixture became homogeneous; the pH was between 8 and 9. After stirring for an additional 1 h, the bright yellow reaction mixture was washed with chloroform (3 × 300 mL) and then acidified with 10 mL of 12 N hydrochloric acid to a final pH of 2. The aqueous phase turned milky white, a clear oil floated to the top, and a carbon disulfide layer settled to the bottom. Ethyl acetate (300 mL) was added to extract the product; this phase was dried over magnesium sulfate and concentrated by rotary evaporation. The products, which were pure by thin layer chromatography, were obtained in yields of 90–95% as colorless oils which often solidified upon standing. When Etc-L-amino acids **1a** were prepared for subsequent conversion to Dts-L-amino acids **2a**,[2] no further purification was necessary. Recrystallizations can often be effectively performed using benzene–petroleum ether mixtures.[8,19] For example, Etc-glycine and Etc-L-valine prepared by this procedure gave respectively mp 95–97 °C (lit.[8] mp 98–99 °C) and mp 66 °C (lit.[19] mp 65 °C) as well as satisfactory elemental analyses.

General Procedure for Preparation of Ethoxythiocarbonyl (Etc)-L-amino Acid Esters (1b). An amino acid ester hydrochloride, **9** (100 mmol), was suspended in 200 mL of chloroform containing *O*-ethyl *S*-carboxymethyl dithiocarbonate, **10** (19.0 g, 106 mmol), and triethylamine (30 mL, 214 mmol) was added. With the last few drops of triethylamine the reaction mixture became completely homogeneous; it generally took on a darkened or pinkish hue. Progress of the reaction was followed by thin-layer chromatography on silica gel GF plates (250 μm). R_f values in chloroform/acetic acid (19:1) were 0 to 0.3 (starting amino acid ester, streak, strongly ninhydrin positive before and after exposure to HCl vapors), 0.59 (starting xanthate ester, UV positive, ninhydrin negative), 0.65 to 0.75 (product Etc-amino acid ester, UV positive, direct ninhydrin negative, weak positive after heating, strong positive after exposure to HCl vapors). After 24 to 40 h at room temperature, the reaction mixtures were worked up by

washing once each with equal volumes of water (to take out the color and triethylamine hydrochloride salt), 5% sodium bicarbonate (to remove mercaptoacetate), and 0.5 N hydrochloric acid (to remove amino acid ester and excess triethylamine). The chloroform phase was dried over magnesium sulfate and concentrated by rotary evaporation. Products were obtained in yields of 97 to 100%, generally as colorless oils (Etc-L-AlaOMe solidified in 1 day to white crystals, mp 60–62 °C). Only trace impurities were occasionally seen by thin-layer chromatography, and the products were carried over for subsequent reactions without further purification.

Acknowledgments. Dr. Ann Hubbard's participation in a portion of this work is gratefully appreciated, and we thank Dr. R. B. Merrifield for helpful discussions and interest.

Registry No.—**6,** 2905-52-4; **7,** 140-89-6; **8,** 3278-35-1; **9** (R′ = R^2 = CH_3), 2491-20-5; **10,** 25554-84-1; ethyl chloroformate, 541-41-3; sodium chloroacetate, 3926-62-3; glycine, 56-40-6; L-valine, 72-18-4; Etc-glycine, 66270-46-0; Etc-L-valine, 66270-47-1; Etc-L-AlaOMe, 66270-48-2.

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Conjugate Addition of Grignard Reagents to *p*-Nitrotoluene. Competitive Attack of Entering Alkyl Group to Ortho and Para Positions

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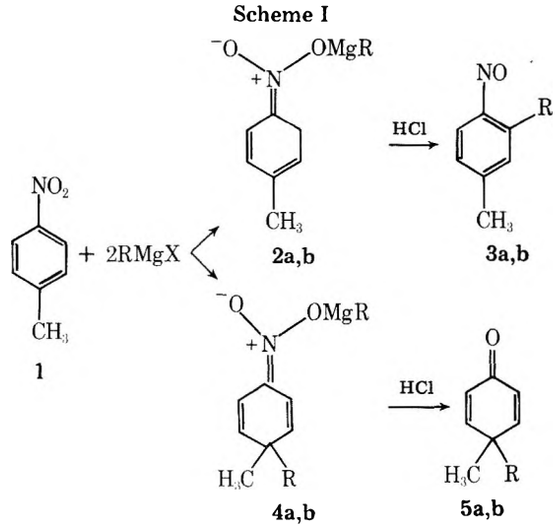
We have recently found[1] that reaction between alkylmagnesium halides and mononitro derivatives of bicyclic aromatic systems proceeds through conjugate addition of RMgX to the nitroarenic system, leading to nitroso compounds alkylated within the aromatic nucleus.

Scheme I



a, R = CH_3; b, R = n-C_4H_9

These results have led us to question the generally held belief[2] that aromatic mononitro compounds undergo 1,2 addition only in reactions with alkyl Grignard reagents.

As preexistent literature data on 1,2 addition were obtained mainly from reactions carried out on monocyclic aromatic systems, while our results were restricted to reactions of bicyclic systems, we were prompted to check the validity of our findings in the case of monocyclic nitroarenes also.

We wish to report now our recent results on reactions of a typical monocyclic substrate such as *p*-nitrotoluene, which show that conjugate addition is predominant with alkyl reagents.

In addition our data indicate that the entering alkyl group has an even likelihood to attack either an alkylated (ipso attack) or a hydrogenated aromatic carbon.

When 2 mol of RMgX were allowed to react for a few seconds with 1 mol of *p*-nitrotoluene (**1**) in tetrahydrofuran or diethyl ether, after addition of aqueous hydrochloric acid two reaction products were isolated in substantial amounts: 2-alkyl-4-methylnitrosobenzene (**3a,b**) and 4-methyl-4-alkyl-2,5-cyclohexadien-1-one (**5a,b**).

The mechanistic pattern of formation of nitroso derivatives such as **3a,b** has been previously described.[1]

Formation of **5a,b** could occur exclusively through a 1,6 addition of RMgX to the nitroarenic system, leading to cyclohexadiene nitronate adducts **4a,b.**

Unlike **2, 4a,b** will not undergo an elimination reaction by addition of hydrochloric acid; therefore they will be hydrolyzed (Nef reaction[3]) to yield **5a,b.**

As shown in the Experimental Section, we were forced to carry out the reaction under conditions considerably milder than those adopted for reactions in bicyclic systems.[1] This was due to the fact that when the reactions were carried out either at room temperature or at 0 °C the yields of **3a,b** and **5a,b** were low, while those in tars were high; in addition small amounts of several unidentified side products appeared.

Yields of nitroso derivatives were larger than those of cyclohexadienone (see Experimental Section). However, if we take into account that the attack in the ortho position is twice as likely as that in the para position, we can conclude that each kind of attack is almost competitive.

The two products can be easily separated by quantitative chromatography on a silica gel column.

Therefore, although the yields of these products are low, our method could represent a reasonable alternative with respect to conventional ways[4] to synthesize cyclohexadienones that require multistage reactions.

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The present results are at variance with previous reports on the reactivity pattern of C_2H_5MgI with nitrobenzene.

Oddo[5] in 1904 reported formation of *N*-ethylaniline and two unidentified distillation fractions.

Conversely, formation of tetrasubstituted hydrazine as the main product was reported by Gilman and McCraken.[6]

No products of N-alkylation were isolated from our experiments.

Comparison of the present findings with our previous data[1] and the ones on reactions with aryl Grignard reagents[7,8] strongly suggest that prevalence of each type of addition will not be dependent upon the aromatic substrate[1c] carrying the nitro group, but it appears to be dependent upon the nature of the Grignard reagent; thus conjugate addition will prevail with alkyl reagents, while with aryl derivatives 1,2 addition takes place.

Finally the ortho and para orientation of the attack with respect to the nitro group confirms the nucleophilic character[1c] of the alkylation process.

Experimental Section

IR, UV, and ^1H NMR spectra were recorded with Perkin-Elmer 275, Perkin 402, and Jeol 60 MHz [$(Me)_4Si$ as internal standard] instruments, respectively.

THF and diethyl ether were purified by distilling under a nitrogen atmosphere after refluxing over sodium. They were stored over sodium wire and distilled from lithium aluminum hydride before using.

Reaction Procedure. A solution of alkylmagnesium halide (0.02 mol) in THF or Et_2O (50 mL) was added dropwise at −70 °C under nitrogen to a solution of *p*-nitrotoluene (0.01 mol) in the same solvent (50 mL). The cooling bath was removed immediately after addition was completed, and 5 mL of aqueous HCl (27%) was added. The reaction mixture was allowed to stir for 1 min and then diluted with cold water. After extraction of the aqueous mixture with CH_2Cl_2, the organic layer was washed several times with water, dried, and evaporated at low pressure. The residue was submitted to chromatographic separation on a silica gel column. Elution with cyclohexane–ethyl acetate (4:1) gave product **3; 3a** (R = CH_3) was obtained free of impurities. It was crystallized from *n*-hexane: mp 39–41 °C dec (lit.[9] 38–41.5 °C) (yield 48–53%);[10] UV ($CHCl_3$) λ_{max} (ϵ) 765 nm (32); IR (CCl_4) 1450 cm^{-1} (N=O); ^1H NMR ($CDCl_3$) δ 2.50 and 3.45 (s, 3 H and 3 H, CH_3 and CH_3), 6.30 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-6), 7.05 (dd, $J_{3,5}$ ~ 2 Hz, 1 H, H-5), 7.45 (d, 1 H, H-3).

3b (R = *n*-C_4H_9) was obtained mixed with 5% of a product which has been tentatively identified from the ^1H NMR spectrum of the mixture as the corresponding nitro derivative. It was purified by chromatography on silica gel using *n*-hexane as eluent.

3b: green oil (yield 45–50%);[10] IR 1450 cm^{-1} (N=O); UV ($CHCl_3$); λ_{max} (ϵ) 765 nm (32); ^1H NMR (CCl_4) δ 0.8–2.20 and 3.75–4.15 (m, 7 H, 2 H, *n*-C_4H_9), 2.45 (s, 3 H, $-CH_3$), 6.15 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-6), 7.00 (dd, $J_{3,5}$ ~ 2 Hz, 1 H, H-5), 7.45 (d, 1 H, H-3).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.65; H, 8.21; N, 8.01.

Further elution of the column with cyclohexane–ethyl acetate (1:1) gave **5** free from impurities.

5a (R = CH_3, yield 11–15%)[10] showed physical and spectroscopic characteristics identical with those reported in literature.[4,11]

5b (R = *n*-C_4H_9, yield 22–25%):[10] pale yellow oil; IR (in film) 1660 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.9 (m, 9 H, *n*-C_4H_9), 1.25 (s, 3 H, $-CH_3$), 6.15–6.75 (AB system, J = 10 Hz, 2 H and 2 H, H-2, H-6 and H-3, H-4).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.05; H, 9.77.

Acknowledgment. This work was carried out with the financial aid of the C.N.R. Rome.

Registry No.—1, 99-99-0; **3a,** 38974-06-0; **3b,** 66270-57-3; **5a,** 1073-14-9; **5b,** 66270-58-4.

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A New and Convenient Synthesis of 1-Aryl-1,2-alkanediones

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The conversion of a methylene group α to a ketone into a carbonyl group to afford a 1,2-dione is an important functional group transformation in organic synthesis.

Numerous syntheses of the title compounds have been reported already, among others oxidation of aryl alkyl ketones,[1,2] alkenes,[3] alkynes,[4] and acylmethylenephenylphosphoranes.[5] By far the most used procedure for the synthesis of α-diketones **5** involved the base-induced α elimination of α-nitrato ketones.[6,7,8] More generally applicable methods for the synthesis of α-diketones involved the use of less general reagents such as *tert*-butoxybis(dimethylamino)methane[10] and pentacarbonyliron.[11] Finally, acetoxylation of β-keto sulfides leads also to 1,2-dicarbonyl compounds.[12]

We wish to report a convenient and mild method for the synthesis of 1-aryl-1,2-alkanediones **5**. Our method can be used in molar quantities and proceeds according to the reaction sequence outlined in Scheme I.

Recently,[13] we described a high-yield synthesis of 1-aryl-2,2-dichloro-1-alkanones **2** involving conversion of alkyl aryl ketones **1** into the corresponding *N*-cyclohexylketimines, which were chlorinated in the α position of the imino function by means of *N*-chlorosuccinimide in carbon tetrachloride at room temperature, the resulting *N*-1-(1-aryl-2,2-dichloroalkylidene)cyclohexylamines being hydrolyzed with aqueous hydrogen chloride solution to the corresponding previously unknown α,α-dichloro ketones **2**.

Treatment of 1-aryl-2,2-dichloro-1-alkanones **2** with sodium methoxide in methanol (2 N solution) at room temperature for a short time (1 h) afforded a mixture of isomeric α,α-dimethoxy ketones, namely 1-aryl-2,2-dimethoxy-1-alkanones **3** and 1-aryl-1,1-dimethoxy-2-alkanones **4**, the formation of which was explained via an epoxide intermediate **6** (Scheme II).[14] The ratio **3**/**4** was dependent on the substitution of the substrate (R, R′), the concentration of the nucleophile, and the temperature control.[14] In general the ratio varied between 40:60 for **3d**/**4d** and 70:30 for **3b**/**4d**. Acidic hydrolysis of this mixture of isomers **3** and **4** with 8 N aqueous hydrogen chloride solution provided pure 1-aryl-1,2-alkanediones **5** in high yields.

It is stressed that all steps of the pathway mentioned here proceed cleanly and that all intermediate compounds may be obtained in very high yields. Starting from ketones **1**, the three-step conversion into α,α-dichloro ketones **2** was exe-

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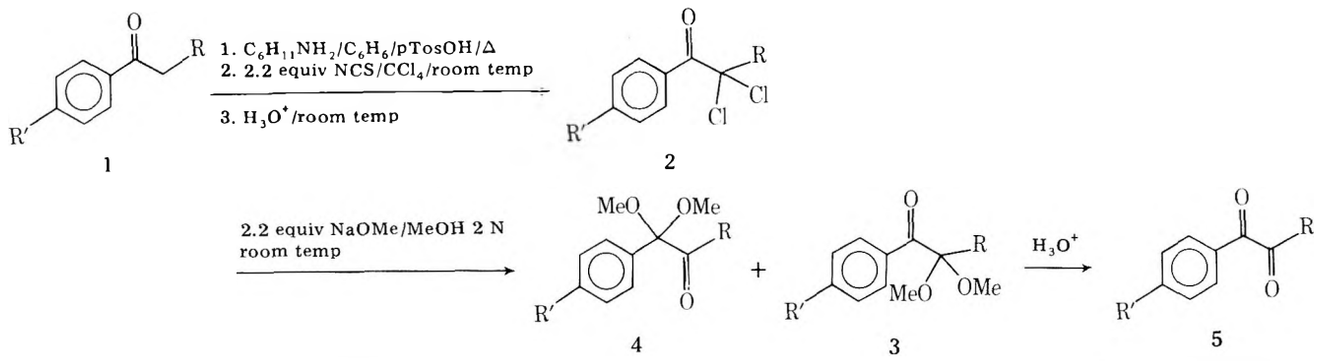
Scheme I



1 2 4 3 5

Scheme II

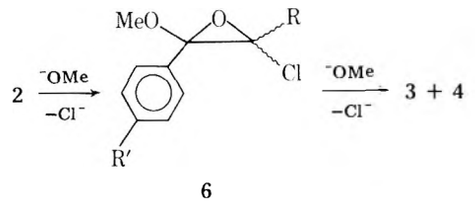


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Table I. Synthesis[a] of 1-Aryl-1,2-alkanediones 5

	R	R′	% yield 1 → 2	% yield 2 → 3, 4	% yield 3, 4 → 5	Bp (5), °C (mmHg)
5a	Me	H	81	94	95	55–58 (0.2)[b]
b	Me	Cl	95	94	94	54–59 (0.03)[c]
c	Et	H	80	98	96	126–132 (12)[d]
d	*n*-Pr	H	90	95	98	60–61 (0.05)[e]

[a] Isolated yields (distillation in vacuo). [b] Lit. bp 55–56 °C (0.3 mmHg) (ref 6). [c] Lit. bp 140–144 °C (20 mmHg) (ref 15). [d] Lit. bp 74–76 °C (0.5 mmHg) (ref 6). [e] Lit. bp 82–84 °C (3 mmHg) (ref 6).

cuted in 80–95% isolated yield (after high vacuum distillation), while the reaction of **2** with NaOMe/MeOH gave α,α-dimethoxy ketones **3** and **4** in 94–98% isolated yield. Finally 1,2-diones **5** were obtained in 94–98% yield. The yields of the respective steps are tabulated below (Table I).

According to the results shown in Table I, the overall yields vary between 72 and 84%, taking into account that all intermediate compounds have been isolated by vacuum distillation.

It was possible to increase the yield of α-diketone **5** by carrying out the reaction sequence **1** → **5** without distillation of compounds **2**, **3**, and **4**. According to this straightforward procedure 1-phenyl-1,2-propanedione (**5a**) was prepared in 85% yield, thus giving rise to an increase in yield of 13% with respect to the results in Table I.

Except for the results described in this paper, almost no information is available on the reaction of α,α-dihalogenoaryl alkyl ketones with nucleophilic reagents. It has been reported[16,17] that the reaction of 2,2-dichloroacetophenones **2** (R = H; R′ = H or Ph) with sodium methoxide in methanol afforded 2,2-dimethoxyacetophenones **3** (R = H; R′ = H or Ph), while it has been later shown[18] that the reaction products involved in this reaction were their isomeric structures **4** (R = H), i.e., 2,2-dimethoxy-2-phenylacetaldehydes. The mistakenly attributed *p*-phenyl-2,2-dimethoxyacetophenone (**3**, R = H; R′ = Ph) could be further converted into *p*-phenylphenylglyoxal by acidic hydrolysis.[17]

The latter three papers mentioned reactions of 2,2-dichloroacetophenones, which are easily accessible.[19] The higher homologues **2** (R ≠ H) were previously unknown and are now generally available by the reaction sequence **1** → **2** outlined above. In contrast to 2,2-dichloroacetophenones **2** (R = H; R′ = H or Ph)[17,18] the methoxide-induced rearrangement of the higher homologues **2** (R = alkyl) via an intermediate epoxide gave rise to a mixture of isomeric α,α-dimethoxy ketones, which were hydrolyzed to the parent α-diketones.

In conclusion, the introduction of a carbonyl group in the α position of a carbonyl function conjugated with an aryl nucleus, according to the method described here, proceeds under relatively mild conditions and in high yields. The method, however, is limited to alkyl aryl ketones **1**. Nevertheless, the 1-aryl-1,2-alkanediones **5** thus available are important intermediates in organic syntheses (e.g., compound **5a** is the well-known precursor of ephedrine).

Experimental Section

All starting materials used were commercially available. IR spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were measured with a Varian T-60 apparatus, while mass spectra were obtained from a GC–MS coupling of a Pye-Unicam gas chromatograph (model 104; SE 30; 1.5%; 1.5 m; He carrier gas) with an AEI MS 20 mass spectrometer. GLC analyses were performed with a Varian Model 920 gas chromatograph (SE 30; 5%; 3 m; H_2 carrier gas).

Synthesis of 1-Aryl-1,2-alkanediones 5. The experimental procedure used for the synthesis of 1-phenyl-1,2-pentanedione (**5d**) is representative of all other preparations. From 20.0 g (0.123 mol) of valerophenone (**1d**) there was obtained 24.9 g of 2,2-dichloro-1-phenyl-1-pentanone (**2d**; 90%), bp 73–79 °C (0.06 mmHg).[13] To 118.5 mL of 2 N sodium methoxide in methanol (0.237 mol, 2.2 equiv) cooled in a water bath was added dropwise with stirring 24.9 g (0.108 mol) of 2,2-dichloro-1-phenyl-1-pentanone (**2d**). After stirring 1 h at ambient temperature, methanol was evaporated under vacuum. Addition of 100 mL of water and extraction three times with diethyl ether yielded, after drying ($MgSO_4$) and evaporation, a clear oil which was distilled to afford 22.8 g of a pale yellow oil, bp 69–71 °C (0.05 mmHg) (40% **3d** and 60% **4d** as shown by NMR and GLC[20]). A solution of 22.8 g (0.1027 mol) of **3d** and **4d** in 200 mL of CCl_4 was vigorously stirred with 100 mL of concentrated HCl and 50 mL of water. After stirring overnight, the organic phase was isolated, washed with water, dried ($MgSO_4$), evaporated in vacuo, and distilled to give 17.7 g of 1-phenyl-1,2-pentanedione (**5d**), bp 60–61 °C (0.05 mmHg) (98% yield starting from **3d** + **4d**). The reaction sequence outlined in Scheme I was performed without purifying the intermediates by distillation. This synthesis was carried out on a large scale. Starting from 67.0 g of propiophenone (**1a**) there was obtained 63 g of 1-phenyl-1,2-propanedione (**5a**; 85% yield).

Acknowledgment. We are indebted to the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek" for financial support to the Laboratory.

Registry No.—**1a**, 93-55-0; **1b**, 6285-05-8; **1c**, 495-40-9; **1d**, 1009-14-9; **2a**, 57169-51-4; **2b**, 57169-53-6; **2c**, 66255-85-4; **2d**, 66255-86-5; **3a**, 38868-78-9; **3b**, 32763-17-0; **3c**, 57205-27-3; **3d**, 66255-87-6; **4a**; 57711-28-1; **4b**, 64743-30-2; **4c**, 66255-88-7; **4d**, 66255-89-8; **5a**, 579-07-7; **5b**, 10557-21-8; **5c**, 3457-55-4; **5d**, 20895-66-3.

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(20) Compound **4d** had a lower R_f value than compound **3d** (GLC). Benzoyl derivative **3d** showed a carbonyl stretching vibration at 1701 cm^{-1}, while isomer **4d** exhibited a much higher value at 1733 cm^{-1}. The NMR data of **3d** and **4d** supported the respective structural assignment. NMR (CCl_4) of compound **3d**: δ 0.83 (t, 3, J = 6 Hz, CH_3), 1.2 (m, 2, CH_2Me), 1.9 (t, 2, J = 7 Hz, $CH_2CC{=}O$), 3.25 (s, 6, $(OMe)_2$), 7.8–8.2 (m, 2, ortho aromatic protons), 7.2–7.5 (m, 3, meta and para aromatic protons). NMR (CCl_4) of compound **4d**: δ 0.76 (t, 3, J = 6.5 Hz), 1.30 (sextet, 2, CH_2Me), 2.40 (t, 2, $CH_2C{=}O$), 3.18 (s, 6, $(OMe)_2$), 7.2–7.6 (m, 5, C_6H_5). The mass spectral fragmentation further established the identity of acetals **3d** and **4d**. Mass spectrum of **3d**: *m/e* (rel abundance) no M^+, 117 (100), 105 (21), 77 (18), 71 (18), 57 (9), 43 (42). Mass spectrum of **4d**: *m/e* (rel abundance) no M^+, 151 (100), 105 (36), 91 (12), 77 (24), 59 (12), 51 (8), 43 (8).

Oxygen-18 Exchange between $[^{18}O]H_2O$ and H_2O_2 in the Presence of FSO_3H

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A peroxide molecule may undergo a variety of chemical reactions. The chemical versatility of peroxides is due to the fundamentally different cleavage modes available to the peroxide structure. While the free-radical chemistry of peroxide involving the homolytic cleavage of the weak O–O bond under a variety of conditions is well documented, the heterolytic cleavage of the O–O bond of peroxide is poorly understood in the mechanistic level.[1-3]

The unimolecular heterolytic cleavage of a peroxide molecule would generate RO^+ (oxenium ion) species, which is expected to be extremely reactive and for whose existence in solution there is no convincing evidence.[4] The bimolecular nucleophilic substitutions of peroxides with carbon, nitrogen, sulfur, phosphorus, and halide nucleophiles are well-known, and acid catalysis in these reactions has been observed.[2,3]

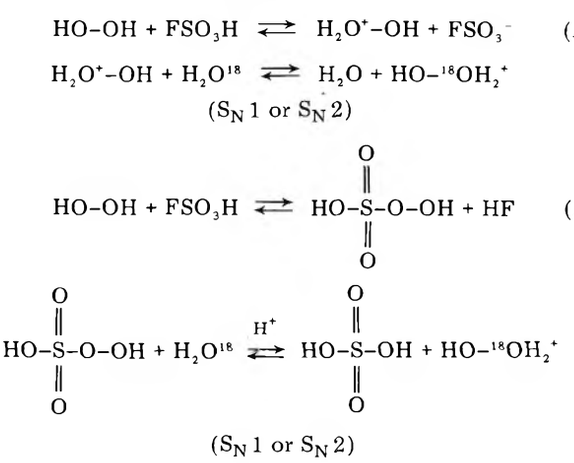
Although water is a reasonably good nucleophile in its attack on sp^3 carbon, its nucleophilic reaction with peroxides is not yet known. The lack of reactivity is normally explained in terms of the repulsion between the electrons on the incoming oxygen nucleophile and those on the peroxide oxygen.[2] Thus it was reported that no exchange occurs under acidic conditions between $[^{18}O]H_2O$ and either hydrogen peroxide,[5] alkyl hydroperoxides,[5] or peroxy acids[6] or between $[^{18}O]$ alcohols and hydrogen peroxide.[7] Similarly, hydrogen peroxide and alkyl hydroperoxides do not undergo oxygen isotope exchange with $^{18}OH^-$.[3]

Table I. $[^{18}O]$ Exchange of H_2O_2[f] with $[^{18}O]H_2O$[a]

run	H_2O_2, μL[b]	FSO_3H,[h] μL	$[^{18}O]H_2O$, μL[c]	Time, days	% exchange[d]
1	140	290	90	1.5	3.7
2	100	260	100	3.5	16.3
3	160	260	100	3.5	33.0
4	70	460[e]	50	3.0	<2.0

[a] Experiments were run by mixing the components in a Pyrex glass vessel under N_2 atmosphere at room temperature in the dark for the indicated time and by successively evacuating the system and treating with solid $KMnO_4$. O_2 evolved was trapped and analyzed for the ratio of *m/e* 34/32 by a mass spectrometer (Hitachi RMU-6 at 25 eV). Runs showing the presence of appreciable N_2 in the sample were discarded. [b] 90% H_2O_2. [c] Atom enrichment was determined to be 78% by mass spectrometric analysis. [d] The ratio of *m/e* 34/32 after correcting for the initial enrichment. The error limit of the measurement is about 1%. [e] Concentrated H_2SO_4 was used instead of FSO_3H. [f] Registry no. 7722-84-1. [g] Registry no. 14314-42-2. [h] Registry no. 7789-21-1.

Scheme I



In connection with our interest in oxygenase-catalyzed reaction mechanisms, we had an opportunity to reexamine the possibility of oxygen isotope exchange between $[^{18}O]H_2O$ and H_2O_2 in the presence of fluorosulfonic acid,[8] the strongest of the simple protonic acids, and wish to report the results of our work.

The results indicated by Table I demonstrate clearly that under these conditions water is a good enough nucleophile to cleave the O–O bond of hydrogen peroxide or its derivative. There appear to be two possible mechanisms for the exchange (Scheme I). Control experiments in which aliquots of the total mixture were analyzed for $SO^{16}O^{18}/SO^{16}O^{16}$ (*m/e* 66/64) prior to oxidation with $KMnO_4$ indicated that both concentrated H_2SO_4 and FSO_3H readily exchange oxygen isotope with $[^{18}O]H_2O$. However, only in the presence of FSO_3H does H_2O_2 exchange oxygen isotope with $[^{18}O]H_2O$. Therefore, it may be concluded that if mechanism (A) is operating, hydrogen peroxide is not significantly protonated by concentrated H_2SO_4, while if mechanism (B) is operating,[9] H_2O_2 and concentrated H_2SO_4 do not generate a significant concentration of persulfuric acid. Furthermore, distinguishing between the S_N1 and S_N2 processes is not possible based on the currently available information.

Acknowledgment. We are grateful to Research Corporation and Texas A&M University for their financial assistance and to Professor A. I. Scott for the gift of $[^{18}O]H_2O$ and encouragement.

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Communications

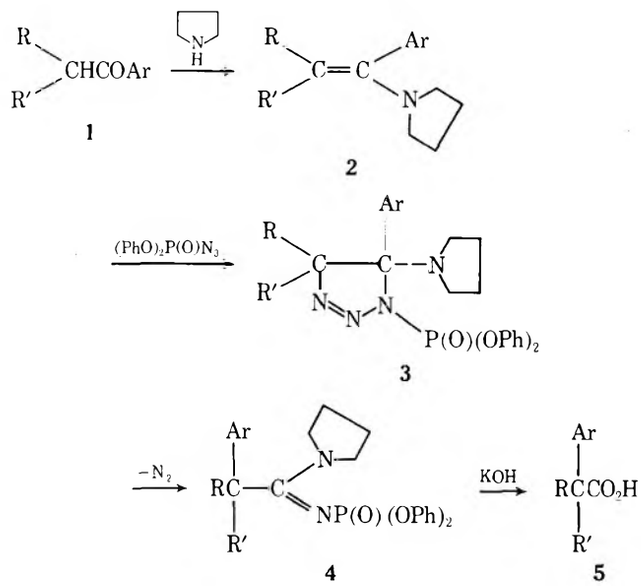
New Methods and Reagents in Organic Synthesis. 2.[1] A Facile Conversion of Alkyl Aryl Ketones to α-Arylalkanoic Acids Using Diphenyl Phosphorazidate. Its Application to a New Synthesis of Ibuprofen and Naproxen, Nonsteroidal Antiinflammatory Agents

Summary: α-Arylalkanoic acids are conveniently prepared from alkyl aryl ketones by the successive treatment with pyrrolidine, diphenyl phosphorazidate (DPPA), and potassium hydroxide; the method has been efficiently applied to a new synthesis of ibuprofen and naproxen, important nonsteroidal antiinflammatory agents.

Sir: Recent publications from these laboratories[1,2] and others[3,4] have revealed that diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$) may be used for various synthetic reactions. The 1,3-dipolar character of DPPA has been well demonstrated by its reaction with enamines of cyclic ketones, which has offered a new method of ring contraction.[2]

We now wish to report a convenient conversion of alkyl aryl ketones 1 to α-arylalkanoic acids 5 using DPPA as a 1,3-dipole in the key step. The new general method consists of three-step operations involving: (1) conversion of alkyl aryl ketones **1** to pyrrolidine enamines **2**; (2) 1,3-dipolar cycloaddition of DPPA to enamines **2** followed by aryl migration with concomitant evolution of nitrogen from labile triazoline intermediates **3**; and (3) hydrolysis of the resulting *N*-phosphorylated amidines **4**, as summarized in Scheme I.

Scheme I



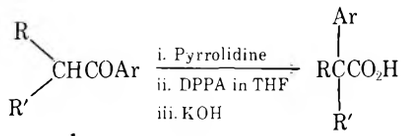
Although similar conversion of alkyl aryl ketones to esters of α-arylalkanoic acids by oxidative rearrangements utilizing thallium(III) nitrate has been reported recently,[5] the present method possesses such advantages that: (1) the functional specificity of the reactions may be much superior; (2) nonoxidative and less toxic reagents[6] can be used; and (3) all the transformations may be readily carried out in multigram quantities using a single reaction vessel.

Condensation of alkyl aryl ketones **1** with pyrrolidine smoothly proceeded in refluxing benzene or toluene in the presence of boron trifluoride etherate[7] to give enamines **2**. Addition of DPPA to enamines **2** in tetrahydrofuran (or ethyl acetate), followed by refluxing the reaction mixture, generated nitrogen to yield *N*-phosphorylated amidines **4** by aryl migration. The intermediates of this transformation are obviously 1,3-dipolar cycloadducts **3**.[2] Although optimum conditions for the reaction have yet to be established,[8] the data in Table I[9] reveal that preparatively useful yields can be obtained under relatively mild conditions.

A typical procedure is as follows. To pyrrolidine enamine **2** (R = Me; R′ = H; Ar = Ph) (3.05 g) in tetrahydrofuran (45 mL) was added with stirring DPPA (4.95 g). The mixture was stirred at room temperature for 1 h, at 40 °C for 1 h, and then refluxed for 2 h. After dilution with ethyl acetate and benzene (1:1, 150 mL), the mixture was successively washed with 5% aqueous citric acid, water, saturated aqueous sodium chloride, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The dried solution was evaporated and the residue was purified by column chromatography on silica gel with ethyl acetate and benzene (1:5) to give the *N*-phosphorylated amidine **4** (5.68 g, 80%).

The one-flask procedure, in which the purification of the enamines by distillation was omitted,[10] as well as the use of an argon atmosphere afforded much better overall yields based on the ketones (compare entries 1 and 3). Morpholine and piperidine enamines gave lower yields (entries 4 and 5). Interestingly, neither the methyl enol ether **6**, the enol acetate **7**, nor the silyl enol ether **8** underwent the 1,3-dipolar cycloaddition reaction with DPPA.[2] Furthermore, 1-phenyl-1-propene (**9**) and ethyl 2-cyano-3-hydroxy-3-phenylacrylate (**10**) were also completely unreactive to DPPA. These results exhibit the prominent functional specificity of DPPA as a 1,3-dipole. This specific nature of the process is highlighted

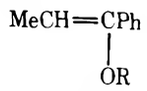
Table I. Conversion of Alkyl Aryl Ketones 1 to α-Arylalkanoic Acids 5



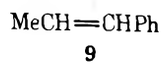
1 5

entry	ketone 1 R	R′	Ar	enamine 2 % yield	amidine 4 % yield	mp, °C	acid 5 % yield
1	Me	H	Ph	79	80	74–76	91
2	Me	H	Ph		81[a]		
3	Me	H	Ph	*b*	84[b,c]		
4	Me	H	Ph	55[d]	63[a]	71–73.5	
5	Me	H	Ph	62[e]	67[a]	67–69	
6	Et	H	Ph	77	74	83–85	91
7	Et	H	Ph		82[c]		
8	Et	H	Ph	*b*	81[b,c]		
9	Me	Me	Ph	*f*	70[c]	87–88.5	quant
10	allyl	H	Ph	79	80[c]	a viscous oil	91
11	Me	H	*g*	*b*	71[b,c]	a viscous oil	92

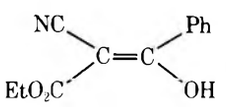
[a] Ethyl acetate was used as reaction solvent. [b] The one-flask procedure.[10] Yields of amidines 4 were based on ketones 1. [c] Reactions were carried out under argon. [d] Morpholine enamine. [e] Piperidine enamine. [f] Prepared according to the literature: W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967). [g] 2-Dibenzofuranyl.



6, R = Me
7, R = MeCO
8, R = Me_3Si



9



10

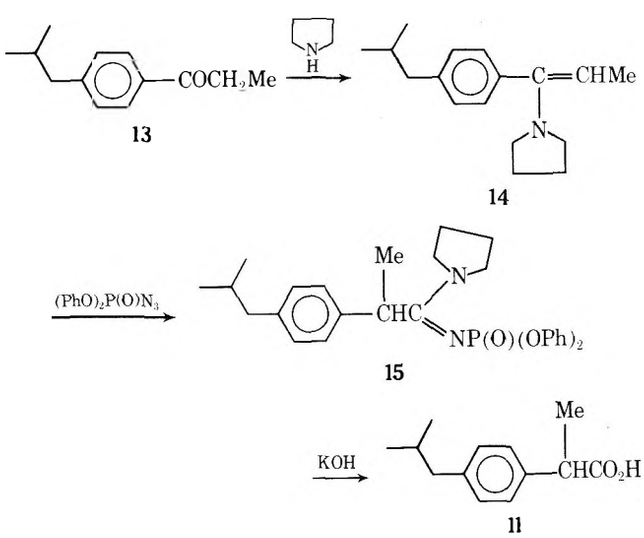
by the successful conversion of the enamine **2** (R = CH_2=$CHCH_2$; R′ = H; Ar = Ph) to the corresponding amidine **4** without any change of the double bond function.[11]

The reaction sequences have been completed by hydrolysis of the *N*-phosphorylated amidines **4** with potassium hydroxide in refluxing ethylene glycol to give α-arylalkanoic acids **5** in good yields.

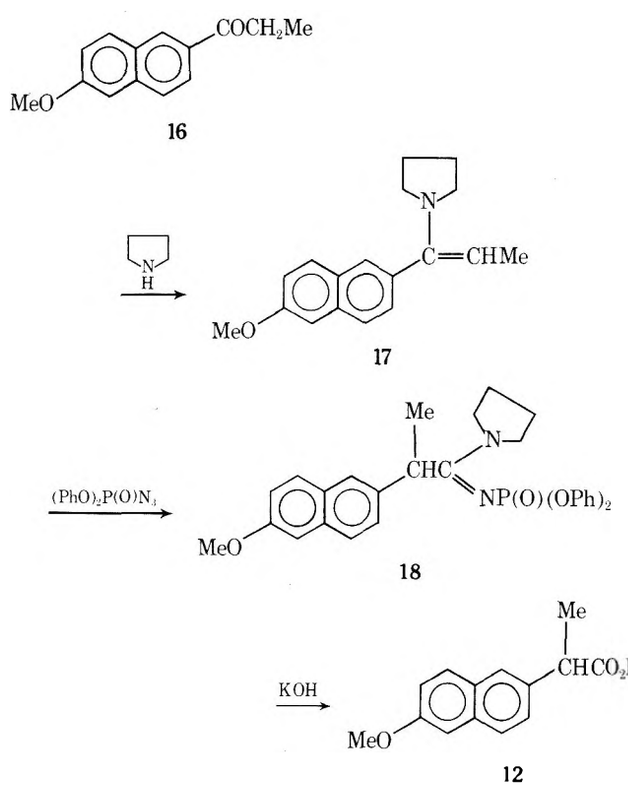
The utility of the above conversions is demonstrated by the efficient synthesis of two important nonsteroidal antiinflammatory agents, ibuprofen (**11**) [2-(4-isobutylphenyl)-propionic acid][12] and naproxen (**12**) [2-(6-methoxy-2-naphthyl)propionic acid].[13] Thus 4-isobutylpropiophenone (**13**), prepared by the Friedel–Crafts acylation of isobutylbenzene with propionyl chloride, was converted to its pyrrolidine enamine **14**, bp 112–114 °C (0.4 mmHg), which further reacted with DPPA under argon to give the *N*-phosphorylated amidine **15**, a viscous oil, in 78% overall yield. Hydrolysis in ethylene glycol gave ibuprofen (**11**) in 79% yield.

Naproxen, though in its racemic form, was also conveniently prepared from ethyl 6-methoxynaphthyl ketone (**16**) by its condensation with pyrrolidine, forming the enamine **17**, bp 148–152 °C (0.2 mmHg), followed by the reaction with DPPA. The resulting *N*-phosphorylated amidine **18**, mp 102.5–105 °C, obtained in 82% yield, was subjected to hydrolysis as above to give naproxen (**12**) in 83% yield.

Current investigations are directed toward the application of the present method to the synthesis of many important medicinal agents bearing α-arylalkanoic acid structures.



13 14 15 11



16 17 18 12

Acknowledgment. We wish to thank Emeritus Professor S. Yamada and Professor K. Koga of University of Tokyo for their interests and discussions.

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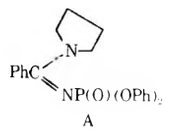

A

(9) All new compounds were fully characterized by NMR and IR spectral means and elemental composition. Known compounds were identified by comparing their physical data (melting or boiling points, IR and NMR spectra) with reported ones.
(10) In the one-flask procedure, the condensation reaction of a ketone **1** with pyrrolidine was carried out as described in the text, and the reaction solvent was removed in vacuo. Tetrahydrofuran was added to the residual crude enamine **2** under argon atmosphere, followed by the addition of DPPA. The reaction and workup were conducted as described in the typical procedure of the text.
(11) Thallium(III) nitrate is reported[5] to be quite reactive to a variety of unsaturated molecules.
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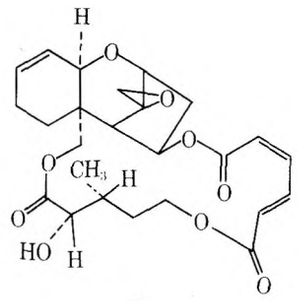
Synthetic Strategy toward Verrucarins. An Approach toward Verrucarol

Summary: The synthesis of a key tetrahydrochromanone intermediate toward a sesquiterpene portion of the verrucarins, potent antitumor agents, involves novel utilization of cyclobutanone annulation, a new approach to creation of α,β-unsaturated-γ-hydroxylated esters, and a new rearrangement.

Sir: The synthesis of the verrucarins such as verrucarin A (**1**), a class of potent antitumor agents, requires consideration of the sesquiterpene portion (cf. verrucarol, **2**) and the attendant macrocycle.[1,2] We wish to report a new approach toward verrucarol which (a) employs cyclopropyl phenyl sulfide to create most of the carbon skeleton except for the cyclohexyl ring, (b) develops a new approach to γ-hydroxylation, and (c)



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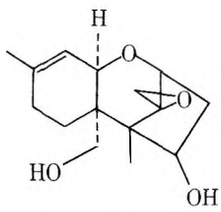

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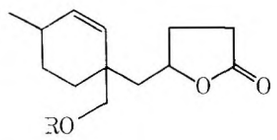


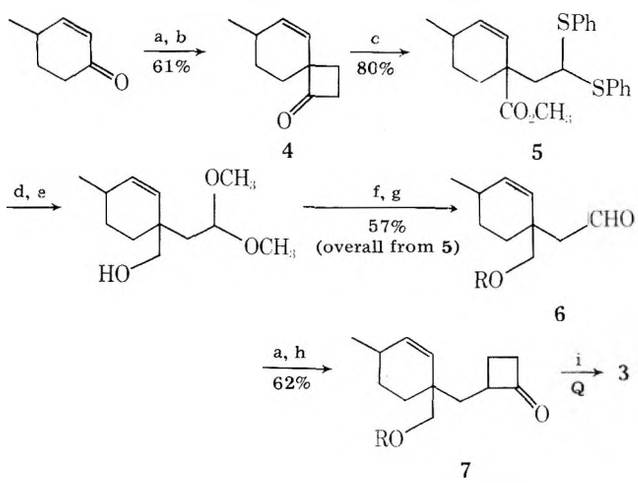
3

illustrates a novel arearrangement to create the tetrahydrochromanone ring system.

Scheme I outlines the synthesis of the key lactone **3**, which contains all of the carbon atoms of **2** save two (methyl group and epoxide methylene). [3.5]Spircannulation of 4-methylcyclohex-2-en-1-one utilizing 1-lithiocyclopropyl phenyl sulfide[3,4] gave the desired cyclobutanone **4**[5] as a mixture of two stereoisomeric adducts (ratio ~1:1). Since this stereochemistry is immaterial with respect to the overall synthesis, no attempt was made to separate the isomers. Secosulfenylation[6] gave the desired ring-cleaved compound **5** in which the geminal carbon was fully elaborated in a functionally differentiated way. Transacetalization, reduction, O-methylation or benzoylation, and hydrolysis prepared the substrate for the final lactone annulation. Cyclobutanone annulation to **7** (R = CH_3 or benzoate)[5] proceeded as before, except that *p*-toluenesulfonic acid in refluxing moist benzene effected the rearrangement of the intermediate cyclopropyl carbinol.[7] Basic hydrogen peroxide[8] completed the synthesis of **3** (R = CH_3 or benzoate).[5] In this case, creation of the lactone via the Baeyer–Villiger oxidation takes advantage of the chemospecificity imparted by the strain of the cyclobutyl ring.

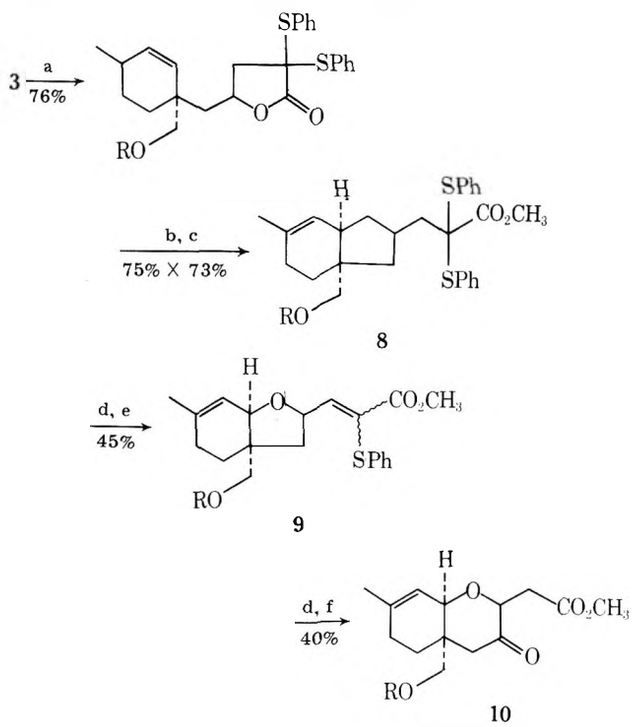
With the completion of the main parts of the carbon skeleton, attention focused upon the adjustment of the oxidation

Scheme I. Synthesis of Lactone 3



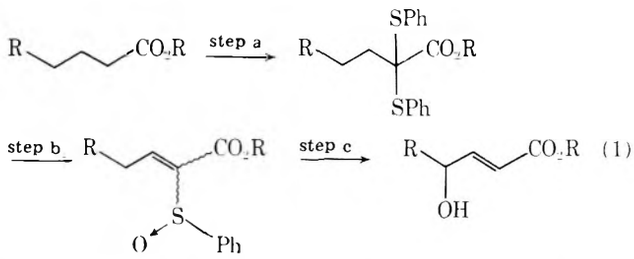
(a) c-$CH_2CH_2C(Li)(SPh)$, THF, 0 °C. (b) HBF_4, H_2O, ether, room temp. (c) $NaOCH_3$, PhSSPh, CH_3OH, reflux. (d) I_2, CH_3OH, reflux. (e) $LiAlH_4$, ether, reflux. (f) NaH, DME, CH_3I or PhCOCl. (g) HCl, H_2O, THF room temp. (h) TsOH, PhH, H_2O, reflux (i) NaOH, H_2O_2, 0 °C.

Scheme II. Preparation of Tetrahydrochromanone



(a) LDA, $PhSSO_2Ph$, THF, −78 → −35 °C. (b) CuBr, $PhCO_3C(CH_3)_3$, PhH, reflux. (c) NaOH, THF H_2O then HCl, H_2O, then CH_2N_2, ether. (d) MCPBA, CH_2Cl_2, −15 °C. (e) CH_2Cl_2, $(CH_3O)_3P$, 46 °C. (f) CH_3OH, DBU, reflux.

level. Initially, the lactone ring was prepared for elaboration of the chromanone by the development of a procedure for the creation of a γ-hydroxyl-α,β-unsaturated system as illustrated in eq 1.[9] The key bissulfenylation (step a)[10] creates the ap-

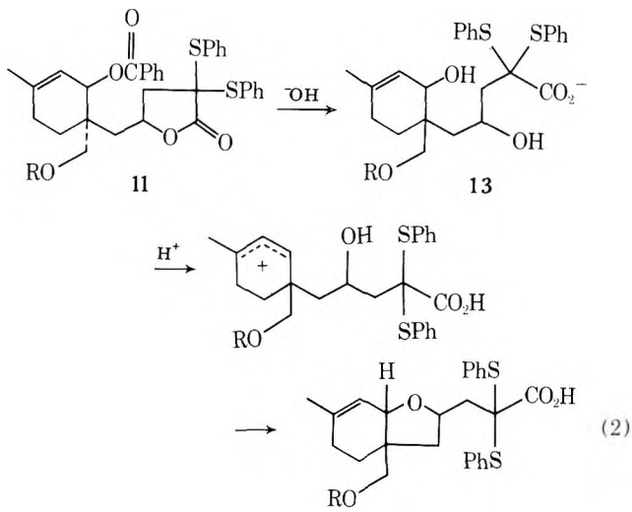


(1)

propriate oxidation level in which it is rearranged by a combination of sulfoxide elimination (step b)[10] and [2,3]sigmatropic rearrangement of allyl sulfoxides (step c).[11]

Bissulfenylation (see Scheme II) proceeded smoothly (step a of eq 1). Before completion of steps b and c, the allylic oxidation of the cyclohexene was carried out. *tert*-Butyl perbenzoate in the presence of cuprous salts[12] avoided oxidation at sulfur and gave high regiochemical control to **11** (see eq 2) as determined by the presence of the vinyl methyl group (δ 1.65), a methine proton (δ 4.5) adjacent to the benzoate, and one vinyl proton (δ 6.15). This compound was normally directly hydrolyzed and acidified, in which case the tetrahydrofuran **8**[5] was isolated. The critical formation of **8** establishes the requisite cis ring juncture for the verrucarol system. The origin of **8** presumably results from solvolysis of the sensitive alcohol **13** and subsequent internal trapping during the acidification, as shown in eq 2. Such internal trappings are known to give high specificity for the cis ring juncture.[13] Thus, the use of the [6.5] ring system rather than the [6.6] one provides the stereochemical control of the ring juncture.

Oxidation and thermolysis of the sulfoxide[10] proceeds

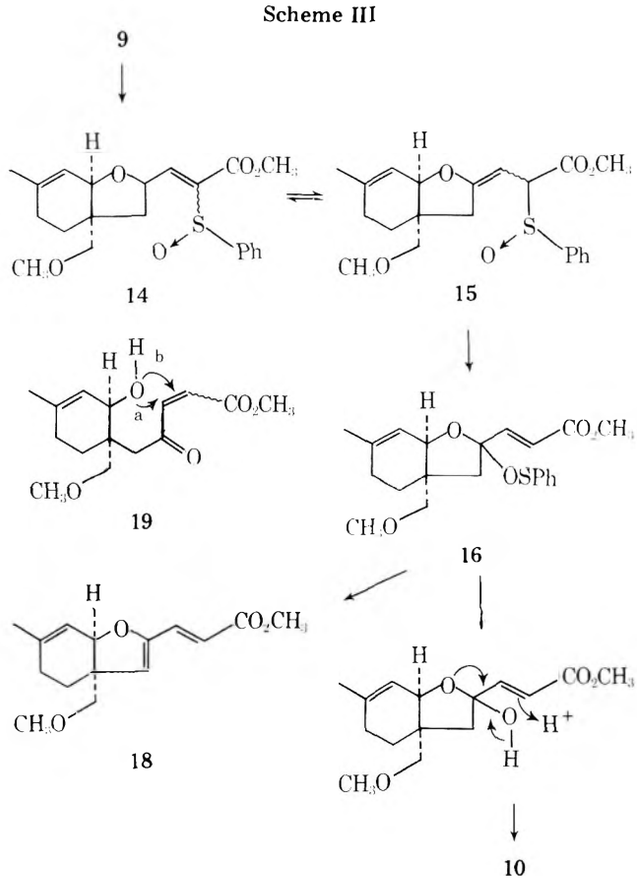


(2)

smoothly to the α-sulfenylated-α,β-unsaturated system **9** (step b of eq 1), which is then oxidized to the corresponding sulfoxide (Scheme III). Base establishes the equilibrium between the vinyl and allyl sulfoxides (**14** ⇄ **15**), in which the latter can suffer [2,3]sigmatropic rearrangement to **16** and in situ desulfenylation to **17**. Isomerization of **17** to **10** involves expansion of a five-membered ring to a six and conversion of a C=C to a C=O; thus, this transformation should be strongly exothermic. Indeed, under these conditions **17** is not isolated but only **10**[5] is observed. Performing this reaction in the absence of a sulfenic ester trap (PhH, $(C_2H_5)_3N$, reflux), only the dihydrofuran **18**,[5] which presumably results from elimination of benzenesulfinic acid in **16**, is observed and is completely homogeneous.

It is tempting to speculate that the rearrangement of **17** to **10** is concerted as represented by the arrows in **17**. Oxygen migrations to electron-deficient carbon are well precedented[14]

Scheme III



as well as embodied in the concept of neighboring group participation of ethereal oxygens in the formation of carbonium ions. Alternatively, **17** would open to **19**, which has the option of reclosing to a six- (path a) or seven-membered ring (path b). The former represents a 6-exo trig (favored) and the latter a 7-endo trig (disfavored) cyclization,[15] which also leads to the expectation of formation of **10**. The tetrahydrochromanone **10** is a mixture of the two epimers at C(2) which could easily be separated. Raphael has worked out a procedure to convert such systems to the trichothecane skeleton of the verrucarols.[2c] Thus, the synthesis of **10** represents the formal completion of the first stage of the verrucarin problem. Work is currently underway to develop alternative approaches to these later stages as well as develop methodology for the macrocyclic ring.

Acknowledgment. We wish to thank the National Institutes of Health (National Cancer Institute) for their generous support of our program.

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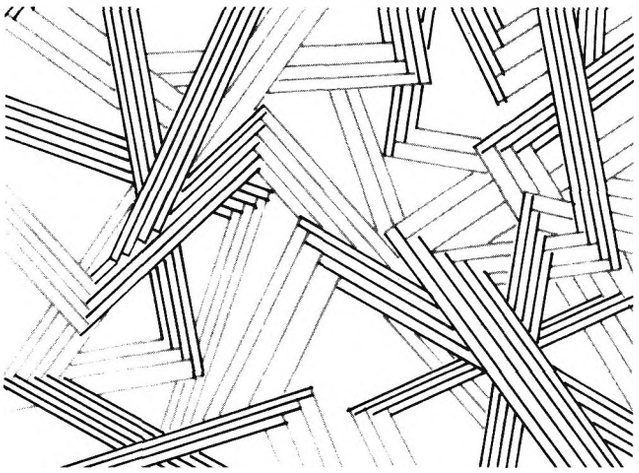

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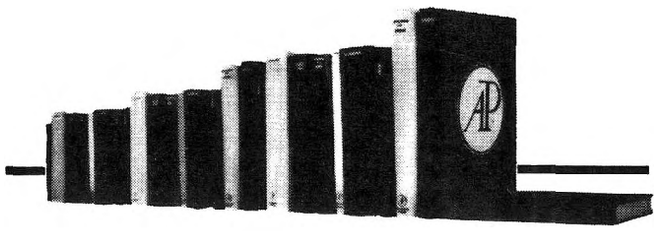

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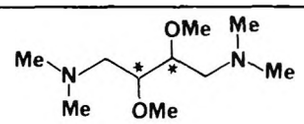

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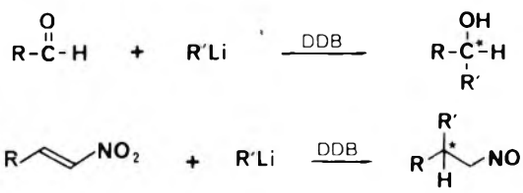
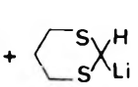
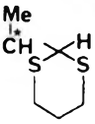
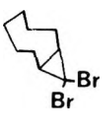
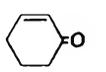
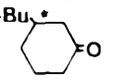


R = alkyl, aryl, vinyl, allyl
R′ = alkyl, aryl, allyl, $RSCH_2$, $(RS)_2CH$, $(RS)_3C$, $RN(NO)CH_2$, $RCOCH_2$

2) Enantioselective Grignard (Mg), Reformatsky (Zn), and Gilman (Cu) reactions (see Table).[4]
3) Photochemical, electrochemical, and alkali-metal pinacolizations of aromatic aldehydes and ketones.[5]

Some specific examples are given in the Table.

Table. Reactions in DDB/pentane at -78°C

Starting Materials	Product	e.e.
PhCHO + *n*-BuLi	Ph-CH(OH)-*n*-Bu	20%
PhCHO + Me-N(NO)-CH_2Li	Ph-CH(OH)-CH_2-N(NO)-Me	15%
PhCHO + CH_2=C(OLi)-NMe_2	Ph-CH(OH)-CH_2-C(=O)-NMe_2	14%
O_2N-CH=C(Me)-H + 	O_2N-CH_2-CH(Me)- 	45%
Me_2N-C(LiO)=C(H)-Me + Ph_2C=O	Me_2N-C(=O)-CH(Me)-CPh_2-OH	20%
 + *n*-BuLi		5%
 + *n*-Bu_2CuLi		10%
Me-C(=O)-Ph + *hν*	Ph-C(OH)(Me)-C(OH)(Me)-Ph	24%

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