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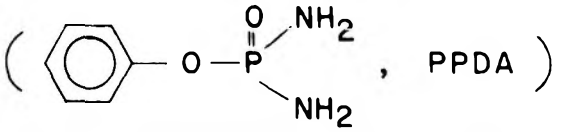
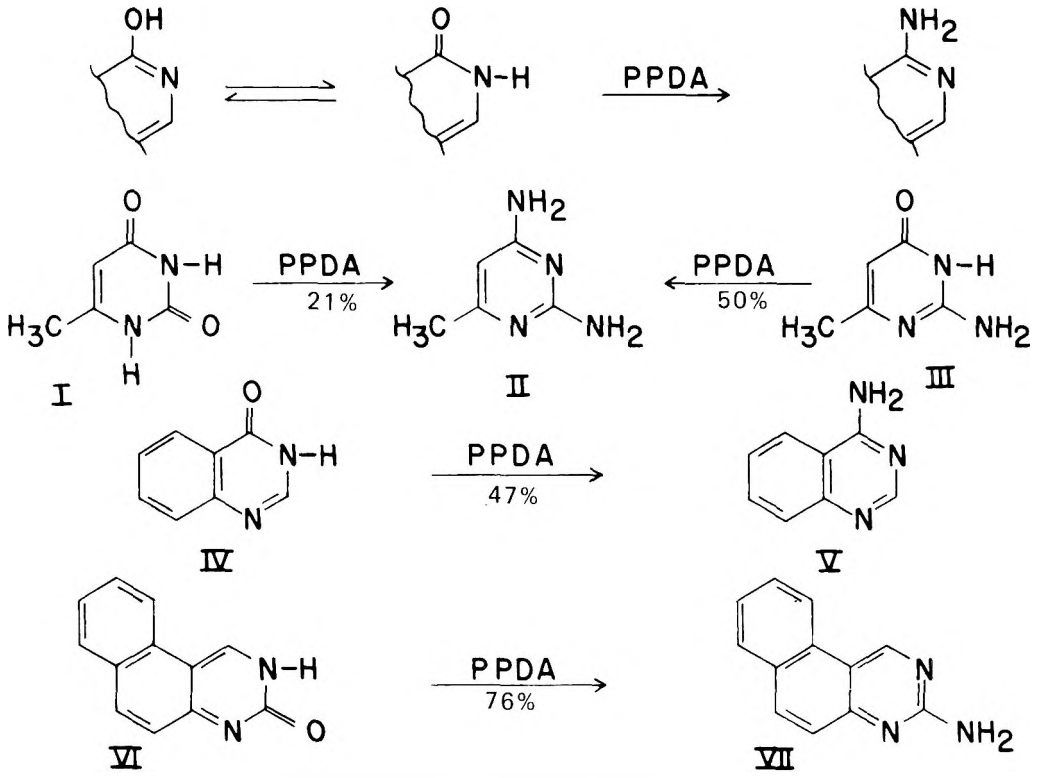
IA ห้องสมุด กรมวิทยาศาสตร์

PHENYL PHOSPHORODIAMIDATE



PPDA Converts Tautomeric Oxo-hydroxy Groups Directly to Amino Groups



OXO DIRECTLY TO AMINO

The classic conversion of oxo groups to amino groups is generally carried out in two steps. First, the oxo group is converted to a halo group by treatment with phosphorous tri- or pentahalide in phosphorous oxyhalide mixtures. The labile halo group is then replaced by amination. While this procedure has been applied successfully to a wide variety of nitrogen heterocycles, undesireable side reactions, functional group displacement, low yields, ring cleavage, and overt failure to react are not uncommon occurrences.

Recently, Arutyunyan and co-workers have reported the direct formation of 2,4-diamino-6-methylpyrimidine (II) by simply heating either 6-methyluracil (I), or 6-methylisocytosine (III) briefly with phenyl phosphorodiamidate (PPDA).[1,2] Similar reactions with N-substituted and N,N-disubstitued phenyl phosphorodiamidates were also reported[3,4,5] and analogous procedures applied to the amination of purines,[3,6,7] N-alkyluracils,[3,8] and s-triazines[1,2]. It was also reported that catalytic amounts of phosphorous oxychloride or amine salts greatly improved the yields.[5,6] More recently, PPDA has been used to convert oxo groups in several fused pyrimidine derivatives directly to the corresponding amino groups.[9] For example, 4-quinazolinone is converted to the corresponding 4-aminoquinazoline in 47% yield, and 3-benzo[f]quinazolinone is converted to 3-aminobenzo[f]quinazoline in 76% yield.

The new PPDA procedure for converting oxo groups to amino groups is potentially as useful as the old classic two step procedure. Furthermore, PPDA is much easier to use and the overall yields are often much improved over the old two step procedure. We think PPDA will prove a useful reagent for converting oxo groups to amino groups in a wide variety of nitrogen heterocycles. In addition, we think PPDA may prove useful for other novel reactions such as converting amides to amidines, or ureas to guanidines. We are just waiting for somebody to give it a try.

(1) E. A. Arutyunyan, V. I. Gunar, E. P. Gracheva, and S. I. Zavyalov, *Izv. Akad. Nauk SSSR, Ser. Khim., 1969*, 655.
(2) N. A. Arutyunyan, V. I. Gunar, and S. I. Zavyalov, *Izv. Nauk SSSR, Ser. Khim, 1970*, 804.
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(7) E. A. Arutyunyan, V. I. Gunar, and S. I. Zavyalov, *Izv. Akad. Nauk SSSR, Ser. Khim., 1970*, 953.
(8) E. A. Arutyunyan, V. I. Gunar, and S. I. Zavyalov, *Izv. Akad. Nauk SSSR, Ser. Khim., 1970*, 1198.
(9) A. Rosowsky and N. Papathanasopoulos, *J. Heterocyclic Chem., 9*, 1235 (1972).

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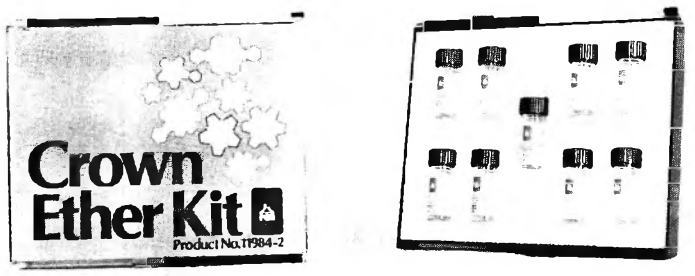

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SEPTEMBER 29, 1978

General Method for the Synthesis of High Enantiomeric Purity Chiral Epoxides[1]

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The Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received May 19, 1978

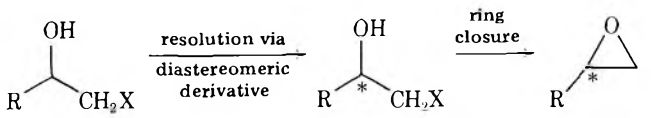
Ring opening of racemic epoxides with thiophenoxide anion affords β-hydroxy sulfides (**3**), which can be resolved by chromatographic separation of their diastereomeric 1-(1-naphthyl)ethylcarbamates (**1** and **2**). Cleavage of either of the carbamate diastereomers with trichlorosilane affords optically pure **3**, which can be converted to the resolved epoxide by S-alkylation followed by treatment with base. Racemic β-hydroxy sulfides are also readily available from the treatment of aldehydes with α-lithioalkyl aryl sulfides.

In view of the large number of stereospecific reactions undergone by epoxides,[2] chiral epoxides of high enantiomeric purity are useful in the synthesis of more complex enantiomerically enriched substances. Because of this utility, many workers have attempted to prepare enantiomerically enriched epoxides. Nevertheless, there are no general synthetic approaches to epoxides of high enantiomeric purity. Two commonly used approaches which warrant mention are asymmetric oxidation and classical resolution.

Numerous asymmetric oxidations of olefins to epoxides have been reported utilizing chiral peracids,[3] chiral phase-transfer catalysts,[4] and chiral transition-metal complexes.[5] Although these are convenient and frequently high yield reactions, the enantiomeric enrichment is often low and not readily predictable. Moreover, the absolute configuration of the predominant enantiomer cannot be reliably assigned from mechanistic considerations.

Alternatively, synthesis of enantiomerically enriched epoxides has been accomplished by optical resolution of an epoxide precursor, generally an alcohol with an appropriate leaving group in the β position, followed by stereospecific epoxide formation (Scheme I).[6] Such approaches can provide epoxides of high enantiomeric purity, but often at considerable expense in time and effort owing to the use of "classical" fractional crystallization techniques for the optical resolutions. Each such resolution is unique, and appropriate resolving agents and conditions must be found by trial and error. Moreover, the enantiomerically pure epoxide precursor has frequently been obtained in low yield since multiple recrystallizations may be necessary to separate the diastereomeric derivatives. These problems can be avoided through the use of multigram LC techniques for the resolution of the epoxide precursor. Our approach to the synthesis of high enantiomeric purity epoxides hinges upon the use of multigram LC.

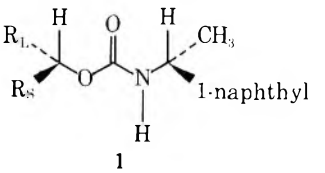
Scheme I



X = Cl, Br, S–*n*-Bu, $N(CH_3)_2$, OAc, OTs, OH

It is known that reaction of enantiomerically pure 1-(1-naphthyl)ethyl isocyanate with a wide variety of racemic secondary alcohols provides diastereomeric carbamate derivatives, **1** and **2**, and that these are frequently separable by liquid chromatography.[7] It is also known that chiral epoxides of high enantiomeric purity can be prepared from resolved β-hydroxy sulfides.[8] If a variety of racemic β-hydroxy sulfides were to prove amenable to resolution using the aforementioned chromatographic approach, a ready, convenient, predictable approach to chiral epoxides of high enantiomeric purity could be realized. Several practical advantages were expected to accrue from this approach.

In nonpolar solvents, diastereomeric carbamates **1** and **2** heavily populate the depicted conformations.[9] The chromatographic separability of the pair appears to derive from the relative ability of R_L and R_S to act in conjunction with the 1-naphthyl group to block the binding of the polar carbonyl



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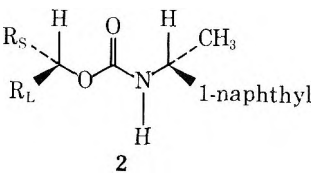


2

region of either diastereomer to the adsorbant. Blocking ability may be either steric or electronic in origin, and various groups have been empirically ranked in terms of effectiveness. Thus, chromatographic separability is more or less predictable. A second consequence of the population of these conformations can be observed in the NMR spectra of **1** and **2**. The magnetic anisotropy of the naphthyl ring causes R_S in **1** to be shielded relative to R_S in **2** (the converse is true for R_L). From the observed chemical shift differences and from the

Table I. Selected NMR and Chromatographic Data for Some Diastereomeric Carbamates

compd	R_L/δ ($CDCl_3$)	R_S/δ ($CDCl_3$)	compd	R_S/δ ($CDCl_3$)	R_L/δ ($CDCl_3$)	α
1a	$CH(CH_3)SPh$/1.27	CH_3/1.21	**2a**	CH_3/1.23	$CH(CH)SPh$/1.27	1.46
1b	CH_2SPh/–	CH_3/1.28	**2b**	CH_3/1.30	CH_2SPh/–	1.25
1c	CH_2SPh/–	CH_3CH_2/0.85	**2c**	CH_3CH_2/0.93	CH_2SPh/–	1.16
1d	Ph/–[a]	CH_2SPh/–	**2d**	CH_2SPh/–	Ph/–[a]	1.30
1e	$CH_3CH_2SCH_2$/–[b]	n-C_8H_{17}/–	**2e**	n-C_8H_{17}/–	$CH_3CH_2SCH_2$/–[b]	1.17
1f[c]	$CH(CH_3)SPh$/1.23	Ph/–	**2f**[c]	Ph/–	$CH(CH_3)SPh$/1.18	1.10
1g[d]	$CH(CH_3)SPh$/1.19	Ph/–	**2g**[d]	Ph/–	$CH(CH_3)SPh$/1.13	1.35
1h[c]	$CH(n$-$C_6H_{13})SPh$/–[a]	C_5H_{11}/–	**2h**[c]	C_5H_{11}/–	$CH(n$-$C_6H_{13})SPh$/–[a]	1.40
1i[d]	$CH(n$-$C_6H_{13})SPh$/–	C_5H_{11}/–	**2i**[d]	C_5H_{11}/–	$CH(n$-$C_6H_{13})SPh$/–[a]	1.25

[a] Nonequivalence observed for $NCHCH_3$: **1d**, δ 1.53; **2d**, δ 1.63; **1h**, δ 1.63; **2h**, δ 1.56; **1i**, δ 1.60; **2i**, δ 1.77. [b] No nonequivalence observed. [c] From *erythro*-**3**. [d] From *threo*-**3**.

known configuration of the amine moiety, the absolute configuration at the carbinol center can be determined.[7] Therefore, spectral differences between the diastereomers allow the determination of absolute configuration and diastereomeric purity of the carbamates.

Results and Discussion

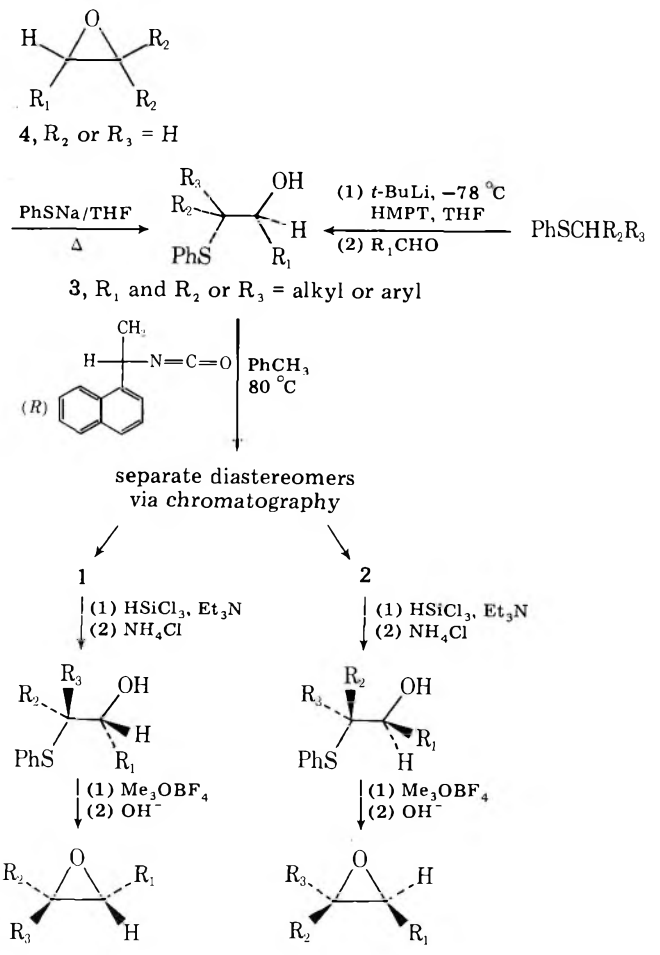
Since the aforementioned chromatographic resolution is most applicable to secondary alcohols,[10] we have utilized secondary alcohols bearing various alkyl or aryl substituents, as well as a β-sulfide function, as models to test the proposed approach (Scheme II). Considerable latitude should be possible in the structure of the thiol reagent utilized in synthesis of the β-hydroxy sulfide. In general, the reagent would be picked for availability, compatability with other functional groups or reagents to be used, ability to impart favorable chromatographic properties (separability and detectability), and ease of purification of the product epoxide. Thiophenol is an obvious choice, although substituted thiophenols may prove useful in selected instances.

The requisite β-hydroxy sulfides (**3**) can be obtained in several ways. If the racemic epoxide is available, ring opening with thiophenoxide, *regioselectivity permitting*, is straightforward. Alternatively, reaction of α-thiolithium reagents (derived from alkyl aryl sulfides)[11] with an aldehyde affords erythro–threo mixtures of **3**. These diastereomers are generally separable by chromatography (neutral alumina, 5:1 hexane–methylene chloride), typically with the threo isomer eluting first.[12] An alcohol inversion sequence as described by Corey et al.[14] permits utilization of an otherwise undersired diastereomer and has the effect of increasing the overall yield of the sequence.

Treatment of **3** with enantiomerically pure 1-(1-naphthyl)ethyl isocyanate yields diastereomeric carbamates **1** and **2**, usually in 80–90% yield. These acid-labile carbamates will decompose on silica gel, but they may be chromatographed on either basic or neutral alumina. Table I shows the observed α values (a measure of chromatographic separability) of some diastereomeric β-hydroxy sulfide carbamate derivatives.

On the basis of conformational arguments earlier presented, the absolute configurations of a number of hydroxy sulfides can be correlated with chemical shift differences between diastereomeric carbamates **1** and **2** (Table I). For example, the chemical shift of the methyl group (R_S) in **1a** is upfield relative to its counterpart in the other diastereomer (R_S in **2a**). From this and the known absolute configuration at the nitrogen-bearing center, the absolute configuration at the carbinyl center of the first eluted diastereomer, **1a**, is assigned as *R*. This is also the configuration expected on the basis of elution order if one makes the reasonable assumption that the $CH(CH_3)SC_6H_5$ substituent will be more effective in warding off adsorption than a methyl group.[15] Elution orders of the remaining pairs of diastereomers in Table I may be rationalized on similar grounds. Indeed, elution orders may be considered as auxiliary sources of configuration information.

Scheme II



Scheme III

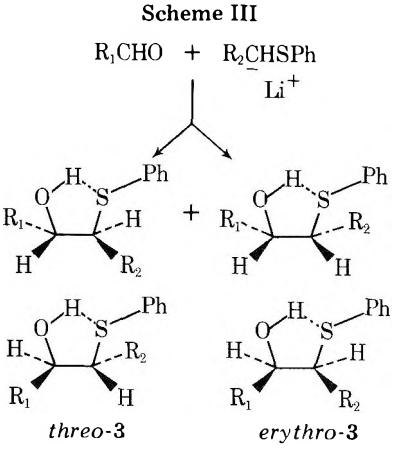


Table II. Optically Active β-Hydroxy Sulfides and Epoxides

hydroxy sulfides[e]				epoxides[f]			
compd	yield, %	$[\alpha]^{25}_{D}$,[a] deg (c 5, $CHCl_3$)	e.e., %[b]	compd	$[\alpha]^{25}_{D}$, deg	yield %	optical purity, %
3b	73	−22.1	~95 ± 5	**4b**	+ 14.0 ± 1.0 (c 0.5, Et_2O)	50[c]	100
3c	92	+57.2	95 ± 5	**4c**	+13.5 (c 5, Et_2O)	95	100
3d	65	+21.2	90 ± 5	**4d**	−41.5 (c 5, PhH)	85	88
3e	89	−22.1	85 ± 5	**4e**	+7.5 (c 5, $CHCl_3$)	94	*d*

[a] In this table, all (+)-**3** are from low R_f carbamates of (*R*)-(+)-1-(1-naphthyl)ethylamine. [b] Estimated from the NMR determined ratio of the diastereomeric carbamates before silanolysis. Spectral congestion causes these determinations to be less certain than usual. [c] GC yield; due to the volatility of the product, only 5–10% was actually isolated pure. [d] Rotational data not previously reported. By analogy, the e.e is expected to be ~85%. [e] Registry no.: **3b**, 67253-47-8; **3c**, 67210-33-7; **3d**, 67210-34-8; **3e**, 67210-35-9. [f] Registry no.: **4b**, 15448-47-2; **4c**, 3760-95-0; **4d**, 20780-54-5; **4e**, 67210-36-0.

After separation, the carbamates are cleaved by silanolysis,[16] using trichlorosilane and an excess of triethylamine (Scheme II). This reaction retrieves the β-hydroxy sulfides in yields of 80–90%. Subsequent treatment of the resolved β-hydroxy sulfide with trimethyloxonium tetrafluoroborate followed by 10% aqueous NaOH provides optically active epoxide **4** of known absolute configuration. This cyclization sequence, completely stereospecific within the experimental error of the optical purity and enantiomeric excess determinations (Table II), involves S_N2 inversion at the reaction center.

Conclusion

By utilizing the chromatographic separability of diastereomeric carbamates derived from β-hydroxy sulfides, it should be possible to prepare a wide variety of optically active epoxides of high enantiomeric purity and known absolute configuration. Both enantiomers are obtained.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were recorded on Varian EM-390 and HR-220 spectrometers at 30 °C. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained on a Varian MAT CH-5 spectrometer. Elemental analyses were performed by M. J. Nemeth and associates, University of Illinois.

General Procedure for the Synthesis of β-Hydroxy Sulfides. A 300 mL three-neck round-bottom flask equipped with an overhead stirrer, addition funnel, N_2 inlet, and reflux condenser was oven-dried and cooled under a stream of dry N_2. Thiophenol (8.0 g, 0.072 mol) in 150 mL of dry tetrahydrofuran was added to the flask, the mixture was cooled in an ice bath, and NaH (4.0 g of a 50% by weight mineral oil dispersion washed with dry pentane to remove the mineral oil) was added in small portions with vigorous stirring. After the evolution of H_2 had ceased, epoxide (0.072 mol) in 50 mL of tetrahydrofuran was added dropwise with stirring at 0 °C. The cold mixture was stirred for 2 h and then heated at reflux for 1–2 h, at which point the suspended matter diasappeared, affording a cloudy solution. Hindred epoxides require longer heating periods, perhaps as much as 10 h. The reaction mixture was cooled in an ice bath and acified with 10% HCl, the THF was removed under vacuum, and the residue was extracted with two 100-mL portions of ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated under vacuum to yield crude β-hydroxy sulfide, which was purified either by fractional distillation at reduced pressure or by crystallization.

3-Phenylthio-2-butanol (3a) was a colorless liquid: bp 98–101 °C (0.9 mm); NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.3 Hz, 3H, CH_3CHS), 1.25 (d, *J* = 7.2 Hz, 3 H, CH_3COH), 2.53 (s, 1 H, OH), 3.23 (d of 1, J_d = 4 Hz, J_q = 6.3 Hz, 1 H, CHS), 3.78 (d of q, J_d = 4 Hz, J_q = 7.2 Hz, 1 H, CHOH), 7.1–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2980, 2940, 2880, 1585, 1480, 1450, 1440, 1380, 1260, 1150, 1000–1100, 910, 750, and 700 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.99; H, 7.74; S, 17.59. Found: C, 66.19; H, 7.90; S, 17.50.

1-Phenythio-2-propanol (3b) was a clear oil: bp 96–99 °C (0.5 mm); NMR ($CDCl_3$) δ 0.92 (t, *J* = 6 Hz, 3 H, CH_3), 1.52 (d of q, *J* = 6 Hz, *J'* = 7 Hz, 2 H, CH_2CH_3), 2.74 and 3.04 (d of AB pattern, J_{AB} = 14 Hz, *J'* = 9 Hz, *J* = 4 Hz, 2 H, SCH_2), 3.1 (broad s, 1 H, OH), 3.6 (m, 1 H, >CH-), 7.0–7.6 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 2980, 2940, 1590, 1480, 1440, 1380, 1030–1130, 940, 740, and 690 cm^{-1}.

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.31; H, 7.23; S, 19.23.

1-Phenylthio-2-butanol (3c) was a clear colorless liquid: bp 109–110 °C (0.6 mm); NMR ($CDCl_3$) δ 0.93 (t, *J* = 7 Hz, 3 H, CH_3), 1.50 (m, 2 H, CH_2CH_3), 2.53 (broad s, 1 H, OH), 2.80 and 3.10 (d of AB pattern, J_{AB} = 12 Hz, *J* = 5 Hz, *J'* = 3 Hz, 2 H, CH_2S), 3.50 (m, 1 H, CHOH), 7.0–7.4 (m, 5 H, Ar); IR (neat) 3200–3600, 3060, 2970, 2930, 2880, 1585, 1480, 1440, 1120, 1070, 740, and 690 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 66.10; H, 7.72; S, 17.81.

1-Phenyl-2-phenylthioethanol (3d) was obtained as a clear oil: bp 165–169 °C (0.4 mm); NMR ($CDCl_3$) δ 2.90 (broad s, 1 H, OH), 3.00 and 3.10 (d of AB pattern, J_{AB} = 13 Hz, *J* = 9 Hz, *J'* = 4 Hz, 2 H, CH_2S), 4.57 (d of d, *J* = 9 Hz, *J'* = Hz, 1 H, CHOH), 7.2 (m, 10 H, Ar); IR (neat) 3200–3600, 3080, 3040, 2940, 1580, 1500, 1480, 1460, 1450, 1200, 1000–1100, 750, and 700 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 230 (20.81), 124 (100), 107 (18.97).

1-Ethylthio-2-decanol (3e) was a clear colorless liquid: bp 101–103 °C (0.05 mm); NMR ($CDCl_3$) δ 3.5–3.7 (m, 1 H, OCH), 2.3–2.8 (m, 4 H, CH_2SCH_2), 1.2–1.5 (m, 14 H, $(CH_2)_7$), 1.25 (t, 2 H, SCH_2CH_3), 0.87 (t, 3 H, $(CH_2)_7CH_3$); IR (neat) 3200–3600, 2900–2980, 2860, 1440–1470, 1380, 1220–1280, and 1000–1080 cm^{-1}; MS (10 eV) (relative intensity) 218 (3.6), 200 (0.7), 138 (7.1), 76 (100), 61 (5.2).

Anal. Calcd for $C_{12}H_{26}SO$: C, 65.99; H, 12.00; S, 14.68. Found: C, 65.58; H, 11.59; S, 14.55.

7-Phenylthio-6-tridecanol (3h and 3i). This compound was prepared as previously described by Dolak and Bryson.[11] To a solution of phenyl 1-heptyl sulfide (5.0 g, 0.022 mol) and hexamethylphosphoric triamide (10 g, 0.055 mol) in 50 mL of tetrahydrofuran at −78 °C was added dropwise 16 mL of *tert*-butyllithium (1.84 M in pentane). The orange solution thus obtained was stirred at −78 °C for 2 h and 2.0 g (2.5 mL, 0.02 mol) of *n*-hexanal in 100 mL of tetrahydrofuran was allowed to drip into the reaction mixture over a period of 1 h. The reaction mixture was then allowed to warm slowly to room temperature and was poured over 50 g of ice; the organic layer was isolated, and the aqueous layer was extracted twice with 50-mL portions of diethyl ether. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue, a mixture of erythro and threo β-hyroxy sulfide (70%), was chromatographed on neutral alumina with hexane/CH_2Cl_2 (4:1) and afforded two major fractions, the threo and then the erythro isomers.

threo-**3h** (12 g) was a high-boiling clear colorless oil: NMR ($CDCl_3$) δ 0.7–1.0 (t, 6 H, terminal CH_3's), 1.0–1.8 (m, 18 H, CH_2's), 2.3 (broad s, 1 H, OH), 2.8–3.1 (m, 1 H, SCH), 3.45 (m, 1 H, OCH), 7.0–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2960, 2940, 2860, 1690, 1590, 1480, 1470, 1440, 1380, 1090, 1030, 740, and 690 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 308 (22.38), 208 (100), 110 (74.94), 55 (43.54).

erythro-**3i** (11 g) was obtained as a clear colorless oil: NMR ($CDCl_3$) δ 0.83 (t, 6 H, terminal CH_3's), 1.0–1.9 (m, 18 H, CH_2's), 2.30 (broad s, 1 H, OH), 2.8–3.2 (m, 1 H, SCH), 3.60 (m, 1 H, OCH), 7.0–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2960, 2930, 2860, 1690, 1580, 1480, 1465, 1435, 1380, 1090, 1020, 740, and 690 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 308 (30.00), 208 (100), 110 (68.72).

1-Phenyl-2-phenylthio-1-propanol (3f and 3 g). This compound was prepared from phenyl ethyl sulfide (15.2 g) and benzaldehyde (11.7 g) by the method used for the preparation of **3h** and **3i.** Distillation, 135–148 °C (0.05 mm), afforded a yellow viscous oil (89%), which was shown by NRM spectroscopy to be a 1:1 erythro–threo mixture. Chromatography of the mixture (neutral alumina, 4:1 hexane–CH_2Cl_2) afforded *threo*-**3f** first and then *erythro*-**3g** as separate 280 nm active bands.

threo-**3f** was, after molecular distillation (100 °C, 0.05 Torr), a clear oil: NMR δ ($CDCl_3$) 7.1–7.5 (m, 10 H, Ar), 4.70 (d, J = 4 Hz, 1 H, CH–O), 3.50 (d of q, J' = 7 Hz, J = 4 Hz, 1 H, CHS), 2.4–2.6 (broad s, 1 H, OH), 1.10 (d, J' = 7 Hz, 3 H, CH_3); IR (neat) 3200–3600, 3070, 3040, 2980, 2940, 2880, 1700, 1590, 1480, 1460, 1380, 1200, 1030, 750, and 700 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}SO$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.62; H, 6.54; S, 13.00.

erythro-**3g** was a clear oil: bp 135–140 °C (0.05 mm); NMR δ ($CDCl_3$) 7.1–7.5 (m, 10 H, Ar), 5.99 (d, J = 8 Hz, 1 H, CH–O), 3.23 (d of q, J = 8 Hz, J' = 7 Hz, 1 H, CHS), 1.07 (d, J' = 7 Hz, 3 H, CH_3); IR (neat) 3200–3600, 3070, 3040, 2980, 2940, 2880, 1700, 1590, 1480, 1460, 1380, 1200, 1030, 750, and 700 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 244 (7.33), 200 (8.77), 138 (100), 137 (49.29), 110 (7.74), 107 (14.26).

Anal. Calcd for $C_{15}H_{16}SO$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.80; H, 6.74; S, 12.34.

General Procedure for the Synthesis of Carbamates. A solution of (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.2 mol) and β-hydroxy sulfide (0.2 mol) in 50 mL of toluene and 1% *N,N*-dimethylethanolamine was heated at reflux until the isocyanate band at 2260 cm^{-1} disappeared. The solvent was evaporated, and the carbamates were chromatographed (3–5 g/run) on a 50 mm × 120 cm column of Brinkmann neutral alumina using 2 L/h of 5:1 hexane–CH_2Cl_2 while monitoring continuously at 280 nm using an ISCO UA-5 absorbance monitor. Three fractions were collected: the first peak which was mainly one diastereomer, a middle fraction which resulted from some overlap of the two peaks (this was recycled), and a second peak which was mostly the low R_f diastereomer. The solvent was removed, and in some instances the carbamates could be recrystallized from hexane–CH_2Cl_2.

1-Methyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 1a was a clear oil: NMR ($CDCl_3$) δ 1.21 (d, 3 H, $OCHCH_3$), 1.27 (d, 3 H, $SCHCH_3$), 3.32 (m, 1 H, SCH), 4.84 (broad d, 1 H, NH), 4.93 (quintet, 1 H, OCH), 5.54 (quintet, 1 H, NCH), 6.82–8.18 (m, 12 H, Ar); IR (neat) 3420, 3080, 2980, 2960, 1690, 1500–1600, 1380, 1200–1260, 1000–1100, 800, 760, and 750 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 379 (0.76), 164 (100), 155 (37.80), 110 (7.14), 77 (5.12), 55 (13.34).

1-Methyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 2a was a clear oil: NMR ($CDCl_3$) δ 1.23 (d, 3 H, $OCHCH_3$), 1.27 (d, 3 H, $SCHCH_3$), 1.57 (d, 3 H, $NCHCH_3$), 3.32 (m, 1 H, SCH), 4.84 (broad d, 1 H, NH), 4.93 (quintet, 1 H, OCH), 5.57 (quintet, 1 H, NCH), 6.82–8.18 (m, 12 H, Ar); IR (neat) 3420, 3060, 2980, 2940, 1710, 1520, 1480, 1380, 1240, 1160, 800, 780, and 750 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 379 (0.97), 164 (100), 155 (38.42), 110 (7.89), 77 (6.00), 55 (13.56).

1-Methyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1b was a white solid: mp 63–65 °C; NMR ($CDCl_3$) δ 1.28 (d, 3 H, $OCHCH_3$), 1.59 (d, 3 H, $NCHCH_3$), 2.7–3.3 (m, 2 H, SCH_2), 4.7–5.1 (m, 2 H, NH and OCH), 5.53 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 365 (0.3), 155 (20.0), 151 (17.5), 150 (100), 109 (6.8); IR (KBr) 3340, 3060, 2980, 1690, 1530, 1380, 1250, 1070, 1040, 800, 780, and 730 cm^{-1}.

1-Methyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2b was a while solid: mp 67–69 °C; NMR ($CDCl_3$) δ 1.30 (d, 3 H, $OCHCH_3$), 1.59 (d, 3 H, $NCHCH_3$), 2.7–3.3 (m, 2 H, SCH_2), 4.7–5.1 (m, 2 H, NH and OCH), 5.53 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 365 (1.0), 155 (36.5), 151 (19.5), 150 (100), 109 (13.4); IR (KBr) 3320, 3080, 2980, 1690, 1540, 1380, 1260, 1240, 1060, 780, 740, and 690 cm^{-1}.

1-Ethyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1c was a white solid: mp 71–73 °C; NMR ($CDCl_3$) δ 0.85 (t, 3 H, CH_2CH_3), 1.94 (d, 3 H, $NCHCH_3$), 1.4–1.8 (m, CH_2CH_3), 2.73–3.18 (m, 2 H, SCH_2), 4.84 (m, 1 H, OCH), 4.95 (broad d, 1 H, NH), 5.59 (quintet, 1 H, NCH), 6.8–8.2 (m, 11 H, Ar); MS (70 eV) *m/e* (relative intensity) 379 (0.2), 164 (100), 155 (19.3), 110 (12.1); IR (KBr) 3380, 3120, 3060, 2980, 1680, 1540, 1250, 1050, 780, 750, and 700 cm^{-1}.

1-Ethyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2c was a white solid: mp 97–98 °C; NMR ($CDCl_3$) δ 0.93 (t, 3 H, CH_2CH_3), 1.58 (d, 3 H, $NCHCH_3$), 1.4–1.8 (m, CH_2CH_3), 2.73–3.18 (m, 2 H, SCH_2), 4.84 (m, 1 H, OCH), 4.95 (broad d, 1 H, NH) 5.59 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 379 (0.6), 164 (100), 155 (47.9), 110 (24.6); IR (KBr) 3380, 3080, 2980, 2940, 2830, 1690, 1545, 1390, 1370, 1250, 1050, 780, and 750 cm^{-1}.

1-Phenyl-2-phenylthioethyl *N*-[1-(1-napthyl)ethyl]carbamate 1d was a white solid: NMR ($CDCl_3$) δ 1.53 (d, J = 7.0 Hz, 3 H, CH_3), 3.23 (m, 2 H, SCH_2), 4.37 (broad s, 1 H, NH), 5.47 (quintet, J = 7.0 Hz, 1 H, CHNH), 5.77 (d of d, J = 6.0 Hz, J' = 11.0 Hz, CHOH), 7.0–8.2 (m, 17 H, Ar); IR (KBr) 3420, 3340, 3060, 2980, 2940, 1720, 1600, 1590, 1500–1550, 1400, 1380, 1200–1250, 1000–1100, 800, 780, 740, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 427 (0.38), 318 (1.08), 212 (100), 155 (53.04), 109 (3.97).

1-Phenyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2d was a white solid: NMR ($CDCl_3$) δ 1.63 (d, J = 7.0 Hz, 3 H, CH_3), 3.18 and 3.23 (d of AB pattern, J_{AB} = 12.0 Hz, J = 9.0 Hz, J' = 6.0 Hz, 2 H, CH_2S), 5.05 (broad s, 1 H, NH), 5.50 (quintet, J = 7.0 Hz, 1 H, $CHCH_3$), 5.77 (d of d, J = 9.0 Hz, J' = 6.0 Hz, 1 H, –CHOH–), 6.9–8.2 (m, 17 H, Ar); IR (KBr) 3420, 3080, 2980, 2930, 1720, 1600, 1585, 1500–1550, 1450, 1440, 1400, 1380, 1210–1260, 1020–1100, 800, 780, 740, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 427 (0.13), 318 (0.29), 212 (100), 155 (70.39).

1-Octyl-2-ethylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1e was a clear colorless oil: NMR ($CDCl_3$) δ 0.87 (t, 3 H, $(CH_2)_6CH_3$), 1.1–1.7 (m, 15 H, $(CH_2)_6$ and SCH_2CH_3), 1.63 (d, 3 H, $NCHCH_3$), 2.4–2.8 (m, 4 H, CH_2SCH_2), 4.86 (quintet, 1 H, OCH), 5.00 (broad d, 1 H, NH), 5.63 (pent, 1 H, NCH), 7.2–8.2 (m, 7 H, Ar); MS (70 eV) *m/e* (relative intensity) 415 (0.16), 215 (15.53), 200 (100), 171 (34.5), 155 (59.0); IR (neat) 3420, 2960, 2940, 2860, 1710, 1510, 1450, 1390, 1370, 1310, 1210–1270, 1060, 800, and 780 cm^{-1}.

1-Octyl-2-ethylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2e was a clear colorless oil: NMR ($CDCl_3$) δ 0.87 (t, 3 H, $(CH_2)_6CH_3$), 1.1–1.7 (m, 15 H, $(CH_2)_6$ and SCH_2CH_3), 1.63 (d, 3 H, $NCHCH_3$), 2.4–2.8 (m, 4 H, CH_2SCH_2), 4.86 (quintet, 1 H, OCH), 5.00 (broad d, 1 H, NH), 5.63 (pent, 1 H, NCH), 7.2–8.2 (m, 7 H, Ar); MS (70 eV) *m/e* (relative intensity) 415 (0.81), 215 (16.1), 200 (100), 171 (36.7), 155 (51.6); IR (neat) 3420, 2960, 2940, 2860, 1710, 1510, 1450, 1390, 1370, 1310, 1210–1270, 1060, 800, and 780 cm^{-1}.

1-Phenyl-2-phenylthio propyl *N*-[1-(1-naphthyl)ethyl]carbamate 1f was a clear oil: NMR ($CDCl_3$) 7.0–8.3 (m, 17 H, Ar), 5.70 (d, 1 H, OCH), 5.56 (quintet, 1 H, NCH), 4.96 (broad d, J = 7 Hz, 1 H, NH), 3.5 (m, 1 H, SCH), 1.64 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.23 (d. J = 6 Hz, 3 H, $SCCH_3$); IR (neat) 3420, 3080, 2980, 2940, 1740, 1600. 1585, 1480–1540, 1450, 1380, 1200–1260, 1000–1100, 800, 780, 750, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (35.0), 155 (100), 138 (49.3), 137 (57.2), 77 (74.8), 127 (27.3), 57 (14.0), 43 (28.8).

1-Phenyl-2-phenythiopropyl *N*-[1-(1-napthyl)ethyl]carbamate 2f was a clear oil: NMR ($CDCl_3$) δ 8.0–7.1 (m, 17 H, Ar), 5.71 (d, J = 7 Hz, 1 H, OCH), 5.57 (quintet, J = 7 Hz, 1 H, NCH), 4.91 (broad d, 1 H, NH), 3.36 (m, 1 H, OCH), 1.64 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.18 (broad peak sharpened to a doublet on warming to 70 °C at 90 MHz, 3 H, $SCCH_3$); MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (46.5), 155 (100), 138 (21.9), 137 (38.2), 77 (23.2), 127 (17.1), 57 (38.9), 43 (28.7); IR (neat) 3420, 3080, 2980, 1740, 1600, (17.1), 57 (38.9), 43 (28.7); IR (neat) 3420, 3080, 2980, 2940, 1740, 1600, 1585, 1480–1540, 1450, 1380, 1200–1260, 1000–1100, 800, 780, 750, and 700 cm^{-1}.

1-Phenyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 1g was a clear oil: NMR ($CDCl_3$) δ 7.0–8.5 (m, 17 H, Ar), 5.90 (d, J = 7 Hz, 1 H, OCH), 5.73 (quintet, J = 7 Hz, 1 H, NCH), 5.15 (broad d, J = 7 Hz, 1 H, NH), 3.5–3.7 (m, 1 H, SCH), 1.67 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.19 (broad d, 3 H, $SCCH_3$); MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (57.4), 155 (100), 150 (25.6), 138 (22.6), 137 (38.4), 110 (5.8), 77 (17.9); IR (neat) 3420, 3060, 2980, 2940, 2880, 1730, 1600, 1580, 1470–1550, 1450, 1400, 1380, 1300–1350, 1200–1260, 1000–1110, 800, 780, 750, and 700 cm^{-1}.

1-Phenyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 2 g was a clear oil: NMR ($CDCl_3$) δ 7.0–8.5 (m, 17 H, Ar), 6.01 (d, J = 5 Hz, 1 H, OCH), 5.26 (broad d, J = 7 Hz, 1 H, NH), 5.20 (quintet, J = 7 Hz, 1 H, NCH), 3.5–3.7 (m, 1 H, SCH), 1.62 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.13 (d, J = 7 Hz, 3 H, $SCHCH_3$); MS (70 eV) 441 (0.2), 226 (97.0), 155 (100), 150 (7.2), 138 (65.6), 137 (82.8), 110 (11.5), 77 (21.5); IR (neat) 3420, 3060, 2980, 2940, 2880, 1730, 1600, 1580, 1470–1550, 1450, 1400, 1380, 1300–1350, 1200–1260, 1000–1110, 800, 780, 750, and 700 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 1 h was a white solid: mp 78–81 °C, NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.80 (quintet, 1 H, NCH), 5.0–5.3 (m, 2 H, NH and OCH), 3.2–3.5 (m, 1 H, SCH), 1.63 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8–1.0 (m, 6 H, terminal CH_3's); MS (70 eV) 505 (0.5), 290 (58.5), 155 (100), 110 (48.9); IR (KBr) 3360, 3060, 2960, 2940, 2880, 1690, 1520, 1390, 1370, 1320, 1240, 1070, 1030, 800, 780, 750, and 690 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 2h was a clear oil: (NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.80 (quintet, 1 H, NCH), 5.0–5.3 (m, 2 H, NH and OCH), 3.2–3.5 (m, 1 H, SCH), 1.56 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8–1.0 (m, 6 H, terminal CH_3's); MS (70 eV) *m/e* (relative intensity) 505 (0.1), 290 (46.8), 155 (100), 110 (36.4); IR (neat) 3420, 3060, 2980, 2940, 2880, 1725, 1480–1550, 1450, 1400, 1380, 1320, 1240. 1060, 800, 780, 750, and 690 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(napthyl)ethyl]carbamate

1i was a clear oil: NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.73 (quintet, 1 H, NCH), 4.7–5.1 (m, 2 H, NH and OCH), 3.5 (m, 1 H, SCH), 1.63 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8 (m, 6 H, terminal CH_3's); IR (neat) 3420, 3200–3400, 3070, 2920, 2880, 1715, 1650, 1450–1570, 1390, 1250, 1210, 1000–1150, 800, and 780 cm^{-1}; MS *m/e* 505.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 2i was a clear oil: NMR ($CDCl_3$) δ 7.2–7.5 (m, 12 H, Ar), 5.73 (quintet, 1 H, NCH), 4.7–5.1 (m, 2 H, NH and OCH), 3.5 (m, 1 H, SCH), 1.53 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's) 0.8 (m, 6 H, terminal CH_3's); IR (neat) 3420, 3200–3400, 3070, 2920, 2880, 1715, 1650, 1450–1570, 1390, 1250, 1210, 1000–1150, 800, and 780 cm^{-1}; MS *m/e* 505.

General Procedure for the Hydrolysis of Carbamates. In a dry 100 mL three-neck flask (equipped with an overhead stirrer, reflux condenser, N_2 inlet, and separatory funnel) was placed 20 mmol of carbamate, 5.1 mL (30 mmol) of triethylamine, and 50 mL of CH_2Cl_2. Trichlorosilane (1.7 mL, 20 mmol) in 10 mL of CH_2Cl_2 was added to the above solution with stirring, and the mixture was then refluxed overnight. The reaction mixture was extracted once with NH_4Cl (saturated) solution, the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography of the residue on neutral alumina with 4:1 hexane–CH_2CL_2 provided pure, optically active β-hydroxy sulfides in quantitative yield.

General Procedure for Synthesis of Optically Active Expoxides from 3. To a stirred solution of 0.01 mol of **3** in 20 mL of CH_2Cl_2 under N_2 was added 1.4 g (0.011 mol) of trimethyloxonium fluoroborate. The mixture was stirred fro 1–2 h until all of the salt dissolved. A condenser was placed on the reaction vessel, and aqueous NaOH (20 mL, 10%) was then added. The mixture was stirred vigorously, and the appearance of epoxide was monitored by GC. When the reaction was over (usually 0.5–2 h), the organic layer was isolated and dried ($MgSO_4$) and the solvent was removed by distillation. The mixture of sulfide and epoxide was purified by either liquid chromatography or preparative GC (15% SE-30 or 15% Carbowax on Chromosorb W).

Acknowledgment. This work was partially supported by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—**1a,** 67210-23-5; **1b,** 67210-24-6; **1c,** 67210-25-7; **1d,** 67210-26-8; **1e,** 67210-27-9; **1f,** 67210-28-0; **1g,** 67253-42-3; **1h,** 67314-18-5; **1i,** 67210-29-1; **2b,** 67210-30-4; **2c,** 67210-31-5; **2d,** 67210-32-6; **2e,** 67238-06-6; **2f,** 67253-43-4; **2g,** 67253-44-5; **2h,** 67253-45-6; **2i,** 67253-46-7; **3a,** 67210-37-1; **3b,** 67253-48-9; **3c,** 67210-38-2; **3d,** 67210-39-3; **3e,** 67210-40-6; **3f,** 67210-41-7; **3g,** 67210-42-8; **3h,** 67210-43-9; **3i,** 67210-44-0; **4a,** 3266-23-7; **4b,** 16033-71-9; **4c,** 55555-96-9; **4d,** 67253-49-0; **4e,** 67210-45-1; thiophenol, 108-98-5; phenyl 1-heptyl sulfide, 13910-15-1; *n*-hexanal, 66-25-1; phenyl ethyl sulfide, 622-38-8; benzaldehyde, 100-52-7; (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, 42340-98-7.

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(12) The elution order of the diastereomers may be rationalized by considering the stereochemical disposition of the substituents during intramolecular hydrogen bonding of the hydroxyl to the sulfur (Scheme III). In such a conformation, the threo isomer has these substituents anti to one another; the erythro isomer has them syn to one another. Thus, the threo isomer is expected to be the most mobile chromatographically, not only on the "warding off" basis advanced for the carbamates[8] but also on the grounds that repulsion between the substituents would cause the erythro isomer to spend relatively less time in the intramolecularly hydrogen bonded form and to hence be relatively more polar toward the absorbent. This argument is similar to one proposed to explain the GC separability of certain diols.[13]
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(15) In the conformations depicted (**1** and **2**), diastereomer **2a** has both effective "warding off" groups, the naphthyl and the $CH(CH_3)SC_6H_5$, on the same face, leaving the other face of the diastereomer relatively accessible to the adsorbent. However, neither face of **1a** is as readily accessible. Hence, **1a** is expected to elute before **2a.** Note that phenyl is more "protective" than $-CH_2SC_6H_5$ in **1d** and **2d** and that $-CH_2SCH_2CH_3$ is more "protective" than n-C_8H_{17}. The steric and electronic composition of a substituent *near the point of attachment* is more important then "remote" structure for relatively nonpolar substituents. Remote polar binding sites would certainly be expected to influence chromatographic behavior. It is evident that such simple concepts could provide a rational basis for engineering chromatographic separability into diastereomeric carbamates.
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Synthesis of Adamantane Derivatives. 41.[1] Synthesis of 9-Thianoradamantane by Carbon–Hydrogen Carbene Insertion Reaction and Carbon-13 Nuclear Magnetic Resonance Spectra of the Related Compounds

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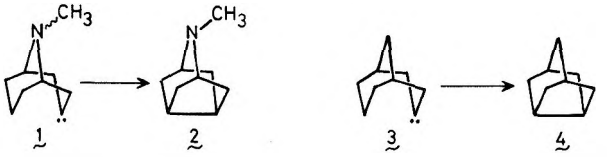
9-Thiabicyclo[3.3.1]nonan-3-one (**6**) was prepared in good yield by treatment of cycloocta-2,7-dienone (**5**) with sodium sulfide in aqueous methanol. Oxidation of **6** with *m*-chloroperbenzoic acid gave the corresponding sulfone (**7**). Reduction of **6** with $NaBH_4$ afforded *endo*-9-thiabicyclo[3.3.1]nonan-3-ol (**8a**). The predominant conformation of **8a** was shown to be chair–boat on the basis of ^{13}C NMR data. Novel skeleton 9-thianoradamantane (**11**) was obtained on pryolysis of the sodium salt of the *p*-toluenesulfonylhydrazone of **6** as the transannular C–H carbene insertion product. **11** was converted to the corresponding sulfone (**13**) and methylsulfonium iodide (**14**).

It is well known that carbene reactions are very useful for the synthesis of bridged or polycyclic compounds as well as cyclopropanes.[2] The usefulness of carbene reactions for the preparation of novel adamantane derivatives is exemplified by the reported synthesis of 2,4-dehydroadamantane,[3] 2,4,6,9-tetradehydroadamantane,[4] and 3-homoadamantene,[5] etc. Previously, we reported the facile synthesis of 9-methyl-9-azanoradamantane (**2**) by the transannular C–H insertion reaction of **1**.[6] A similar reaction of **3** is also known to afford noradamantane (**4**).[7] As an extension of our studies on the



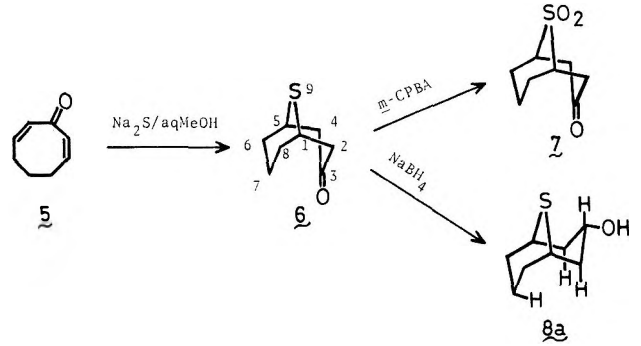
synthesis of adamantane derivatives by utilizing carbenic species, we report in this paper the synthesis of 9-thiabicyclo[3.3.1]nonan-3-one (**6**), its conversion to 9-thianoradamantane (**11**), and ^{13}C NMR spectra of the related compounds.

Results and Discussion

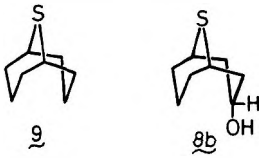
Synthesis, Conformations, and Carbon-13 Nuclear Magnetic Resonance Spectra of 9-Thiabicyclo[3.3.1]nonan-3-one Derivatives. The additions of primary amines and phosphines to cycloocta-2,7-dienone (**5**)[8] are known to afford the corresponding 9-aza- and 9-phosphabicyclo[3.3.1]nonan-3-ones, respectively.[9,10] The addition of hydrogen sulfide to **5** therefore may be one of the most promising and facile routes to 9-thiabicyclo[3.3.1]nonan-3-one (**6**).

In the first attempt, **5** was treated with hydrogen sulfide in chloroform at room temperature overnight, but only **5** was recovered without change. However, treatment of **5** with a 3.3-fold excess amount of sodium sulfide in 80% aqueous methanol at room temperature afforded an adduct **6** as a sublimable solid in 75% yield which was characterized as the desired 9-thiabicyclo[3.3.1]nonan-3-one on the basis of analytical and spectral data. Compound **6** had the anticipated mass spectral molecular ion peak at *m/e* 156 and a strong IR (KBr) absorption at 1695 ($\nu_{C=O}$) cm^{-1}. In the ^1H NMR ($CDCl_3$) spectrum **6** had signals at δ 3.24 (broad s, 2 H, bridgehead protons), 2.81 (AB q, J = 16.8 Hz, $J/\Delta\delta$ = 0.774, 4 H, methylene protons at C_2 and C_4), and 2.35–1.03 (m, 6 H, other protons), and in the ^{13}C NMR spectrum **6** revealed five lines (one singlet, one doublet, and three triplets; Table I), supporting the assigned structure. Oxidation of **6** with *m*-chloroperbenzoic acid afforded the corresponding sulfone **7** in 80% yield, and reduction of **6** with sodium borohydride gave an endo alcohol **8a**, as shown in Scheme I. The assigned stereochemistry and conformation of **8a** were supported by the ^{13}C NMR data (Table I).

Scheme I



The ketone **6** should have a double chair conformation as supported by the appearance of C_7 at 3.8 ppm higher field than C_7 (C_3) of 9-thiabicyclo[3.3.1]nonane (**9**),[11] and hence **6**



should be attacked by borohydride on the exo face to afford the endo alcohol **8a**. The appearance of C_7 of **8a** at 6.0 ppm higher field than C_7 (C_3) of **9** and comparison of the chemical shift (15.6 ppm) with those (14.5 and 15.6 ppm, respectively) of the corresponding 9-aza and 9-phospha analogues[12,13] verified the assigned stereochemistry and chair–boat conformation of **8a**, where C_7 resonates at a high field by the gauche effect as pointed out by Wiseman and Krabbenhoft.[12,13] The double chair conformation of **8b** can not be predominant because of the presence of transannular steric repulsions.[14]

Synthesis of 9-Thianoradamantane (11) by Transannular C–H Carbene Insertion Reaction. The ketone **6** gave the corresponding *p*-toluenesulfonylhydrazone **10a** in 76% yield by the usual procedure. The sodium salt **10b** was obtained on treatment of **10a** with sodium methoxide in methanol, which was dried under reduced pressure and decomposed in refluxing diglyme to afford an 85:15 mixture of **11** and **12** in 67% yield after the usual workup and sublimation. Compounds **11** and **12** were isolated after chromatography on an alumina column and characterized as 9-thianoradamantane, the transannular carbene insertion product, and 9-thiabicyclo[3.3.1]non-2-ene, the hydrogen migration product,

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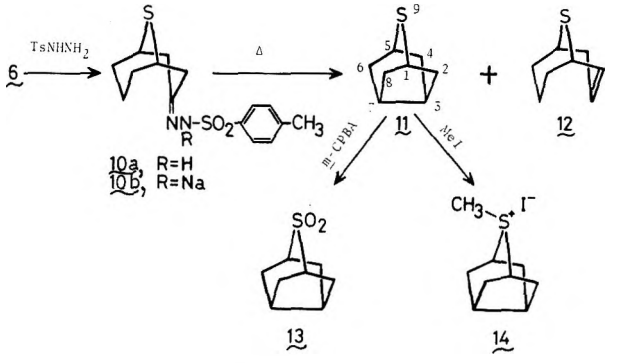
Table I. Chemical Shifts (δ) of 9-Thiabicyclo[3.3.1]nonane and Related Compounds[a]

compd	registry no.	$C_{1,5}$	$C_{2,4}$	C_3	$C_{6,8}$	C_7
6	67194-70-1	35.8 (d)	49.0 (t)	209.5 (s)	33.1 (t)	17.8 (t)
7	67194-71-2	54.3 (d)	44.2 (t)	203.4 (s)	29.8 (t)	15.3 (t)
8a	67194-72-3	32.5 (d)	34.4 (t)[b]	65.3 (d)	33.7 (t)[b]	15.6 (t)
9	281-15-2	33.2 (d)	32.1 (t)	21.6 (t)	32.1 (t)	21.6 (t)
11	67194-73-4	44.8 (d)	46.5 (t)	38.7 (d)	46.5 (t)	38.7 (d)
13	67194-74-5	65.4 (d)	39.0 (t)	35.8 (d)	39.0 (t)	35.8 (d)

[a] Downfield from internal tetramethylsilane in $CDCl_3$, and see the structural formulas for numbering of the carbon atoms. [b] These assignments may be interchangeable.

Scheme II



respectively. Compound **11** had mp 242–243 °C, mass spectral ion peaks at *m/e* 140 (M^+) and 106 ($M - H_2S$), and ^1H NMR ($CDCl_3$) signals at δ 3.08 (broad s, 2 H, C_1 H and C_5H), 2.9–2.4 (m, 2 H, C_3 H and C_7 H), and 2.4–1.55 (m, 8 H, the remaining protons). The ^{13}C NMR spectrum of **11** revealed only three lines at δ 46.5 (t, $C_{2,4,6,8}$), 44.8 (d, $C_{1,5}$), and 38.7 (d, $C_{3,7}$), which were compatible with the assigned skeleton belonging to a C_{2v} point group. The olefinic product **12** had the same IR and ^1H NMR spectra and GLC retention time as an authentic sample prepared by lithium aluminum hydride reduction of 6-chloro-9-thiabicyclo[3.3.1]non-2-ene.[11b]

The pyrolytic decomposition of **10b** without solvent did not improve the yield of **11**, affording a 74:26 mixture of **11** and **12** in 54% yield, but this procedure provides a direct isolation of the products via sublimation.

9-Thianoradamantane (**11**) afforded the corresponding sulfone **13** on oxidation with *m*-chloroperbenzoic acid in 75% yield and 9-methyl-9-thianoradamantanium iodide (**14**) on treatment with methyl iodide in 89% yield, as shown in Scheme II.

All of the above results indicate that the 9-thiabicyclo[3.3.1]nonane system is conformationally very similar to the 9-aza, 9-phospha, and carbocyclic analogues and that the 3,7 C–H carbene insertion reactions are useful also for obtaining 9-thianoradamantane (**11**) as well as previously reported 9-aza[6] and carbocyclic analogues.[7]

Experimental Section[15]

9-Thiabicyclo[3.3.1]nonan-3-one (6). A mixture of cycloocta-2,7-dienone (**5**)[8] (200 mg, 1.67 mmol) and sodium sulfide nonahydrate (1.35 g, 5.62 mmol) in 80% (v/v) aqueous methanol (25 mL) was stirred for 40 h at room temperature. After concentration to ca. 10 mL, the mixture was diluted with water (30 mL) and extracted with dichloromethane (10 mL × 4). The combined extracts were washed with water (10 mL × 2) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was purified by sublimation (150 °C, 0.2 mm) to give **6** as a colorless solid (195 mg, 74.8%): mp 194–197 °C; IR (KBr) 2940, 1695, 1440, and 1100 cm^{-1}; ^1H and ^{13}C NMR, see text; mass spectrum, *m/e* (relative intensity, %) 158 (5.0, M + 2), 157 (9.0, M + 1), 156 (100, M^+), 128 (55.5), 123 (6.5), 113 (14.4), 99 (40.0), 60 (98.5), 54 (97.5), 41 (98.0), and 39 (99.0).

Anal. Calcd for $C_8H_{12}OS$: C, 61.52; H, 7.75. Found: C, 61.27; H, 7.61.

9-Thiabicyclo[3.3.1]nonan-3-one 9,9-Dioxide (7). A mixture of **6** (78 mg, 0.50 mmol) and *m*-chloroperbenzoic acid (85% purity; 223 mg, 1.10 mmol) in dichloromethane (10 mL) was stirred at room temperature for 16 h. The mixture was washed successively with 5% aqueous sodium thiosulfate (5 mL) and 5% aqueous sodium bicarbonate (5 mL × 3) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was sublimed (150 °C, 0.2 mm) to afford **7** as a colorless solid (75 mg, 80%): mp >300 °C; IR (KBr) 1698, 1300, 1120, and 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (broad s, 2 H), 3.08 (AB q, J = 14.5 Hz, $J/\Delta\delta$ = 0.354, 4 H), and 2.65–1.1 (m, 6 H); ^{13}C NMR ($CDCl_3$), see Table I; mass spectrum, *m/e* (relative intensity, %) 190 (2.4, M + 2), 189 (4.4, M + 1), 188 (37.3, M^+), 124 (8.9), 122 (22.2), 97 (20.0), 96 (25.0), 82 (100), 69 (81.7), 68 (98.0), 55 (97.0), 54 (98.5), 42 (99.5), and 39 (96.0).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04; H, 6.43. Found: C, 51.22; H, 6.24.

***endo*-9-Thiabicyclo[3.3.1]nonan-3-ol (8a).** To a stirred and ice-cooled solution of **6** (156 mg, 1.00 mmol) in methanol (5 mL) was added sodium borohydride (189 mg, 5.00 mmol), and the mixture was stirred for 40 h at room temperature and refluxed for 20 min. The cooled mixture was treated with a few drops of acetic acid. The solvent was removed to afford the crude product, which was recrystallized from chloroform–*n*-hexane and sublimed (150 °C, 0.2 mm) to give the alcohol **8a** as a colorless solid (130 mg, 82%): mp 142–145 °C; IR (KBr) 3270, 2940, 1470, 1330, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4–3.7 (m, 1 H), 3.38–2.83 (m, 3 H; 2 H in D_2O), and 2.78–1.02 (m, 10 H); ^{13}C NMR, see text and Table I; mass spectrum, *m/e* (relative intensity, %) 160 (4.0, M + 2), 159 (9.0, M + 1), 158 (100, M^+), 140 (25.0), 125 (27.0), 124 (25.0), 87 (65.0), 55 (90.0), 54 (85.0), 41 (99.5), and 39 (90.0).

Anal. Calcd for $C_8H_{14}OS$: C, 60.71; H, 8.92. Found: C, 60.85; H, 8.78.

***p*-Toluenesulfonylhydrazone (10a) of 6.** A mixture of **6** (156 mg, 1.00 mmol) and *p*-toluenesulfonyl hydrazide (400 mg, 2.15 mmol) in ethanol (5 mL) was heated under reflux for 15 h. The mixture was diluted with water to afford the crude product, which was recrystallized several times from aqueous methanol to give **10a** as colorless crystals (310 mg, 75.9%): mp 160–164 °C; IR (KBr) 3240, 1620, 1595, 1330, 1170, 735, and 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (AB q, J = 8.30 Hz, $J/\Delta\delta$ = 0.248, 4 H), 3.44–2.58 (m, 6 H), 2.87 (broad s, ca. 1 H; disappeared on shaking with D_2O), 2.43 (s, 3 H), and 2.23–1.19 (m, 6 H).

Anal. Calcd for $C_{15}H_{20}N_2O_2S_2$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.25; H, 6.17; N, 8.69.

9-Thianoradamantane (11) and 9-Thiabicyclo[3.3.1]non-2-ene (12). A. Thermal Decomposition of 10b in Diglyme. A mixture of the tosylhydrazone **10a** (310 mg, 0.956 mmmol) and freshly prepared sodium methoxide (65.9 mg, 1.22 mmol) in methanol (6 mL) was stirred for 1 h at room temperature under an argon atmosphere. After the solvent was removed under reduced pressure, the residue was dried up at 45 °C for 6 h under reduced pressure (0.2 mm) to afford the sodium salt **10b**, which was decomposed in refluxing diglyme (10 mL) for 1 h. The cooled mixture was diluted with water (50 mL) and extracted with *n*-pentane (10 mL × 5). The combined extracts were washed with water (5 mL × 5) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was sublimed to afford an 85:15 mixture of **11** and **12** (GLC and ^1H NMR analyses) as a colorless solid (90 mg, 67%). Purification of the mixture on an alumina (Wako basic alumina, grade I) column eluting with *n*-pentane gave **11** (70 mg, 52.2%) and **12** (15 mg, 11.1%). **11** had mp 242–243 °C; IR (KBr) 2965, 2900, 2860, 1450, 1310, 1260, 1085, 955, 778, and 720 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see text and Table I; mass spectrum, *m/e* (relative intensity, %) 142 (5.0, M + 2), 141 (11.0, M + 1), 140 (85.0, M^+), 106 (30.0), 99 (75.0), 98 (87.5), 97 (100), 79 (70.0), 65 (50.0), 41 (90.0), and 39 (87.5).

Anal. Calcd for $C_8H_{12}S$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.54.

Compound **12** had mp 140–143 °C (lit.[11b] mp 143–143.5 °C), and its IR and ^1H NMR spectra and GLC retention time were identical with those of an authentic sample prepared by $LiAlH_4$ reduction of 6-chloro-9-thiabicyclo[3.3.1]non-2-ene.[11b]

B. Thermal Decomposition of 10b without Solvent. The sodium salt **10b**, prepared as above from **10a** (300 mg, 0.925 mmol), was well mixed with Celite 535 (0.5 g) and heated at 155–180 °C under reduced pressure (100 mm) in a sublimation flask to afford the sublimed product (90 mg, 70%), which gave a 74:26 mixture of **11** and **12** as a colorless solid (70 mg, 54%) on resublimation.

9-Thianoradamantane 9,9-Dioxide (13). A mixture of 9-thianoradamantane (**11**) (20 mg, 0.14 mmol) and *m*-chloroperbenzoic acid (85% purity; 70 mg, 0.34 mmol) in chloroform (3 mL) was stirred at room temperature for 24 h. The mixture was washed with 5% aqueous sodium thiosulfate (2 mL) and 5% aqueous sodium bicarbonate (2 mL × 3) and dried (Na_2SO_4). Removal of the solvent and sublimation (130 °C, 18 mm) afforded **13** as a colorless solid (18 mg, 75%): mp >300 °C; IR (KBr) 2960, 1450, 1285, 1110, and 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (broad s, 2 H), 2.80 (broad s, 2 H), and 2.52–1.67 (AB q type m, 8 H); ^{13}C NMR, see Table I; mass spectrum, *m/e* (relative intensity, %) 174 (1.4, M + 2), 171 (2.9, M + 1), 172 (10.5, M^+), 108 (100), 94 (30.2), 92 (68.4), 81 (99.5), 78 (67.0), 66 (63.6), 65 (46.5), 41 (93.0), and 39 (99.0).

Anal Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.00. Found: C, 56.02; H, 6.76.

9-Methyl-9-thianoradamantanium (9-Methyl-9-thiatricyclo[3.3.1.0^{3,7}]nonanium) Iodide (14). A mixture of **11** (15 mg, 0.10 mmol) and methyl iodide (340 mg, 2.4 mmol) in chloroform (3 mL) was heated under reflux for 17 h to afford a precipitate, which was filtered off and dried to give **14** as colorless crystals (25 mg, 89%): mp 242–244 °C dec; IR (KBr) 2925, 1460, 1415, 1300, 1250, 1240, 1085, 960, and 710 cm^{-1}; ^1H NMR (D_2O–$CDCl_3$) δ 3.87 (broad s, 2 H), 2.84 (s, 3 H), and 3.0–1.8 (m, 10 H).

Anal. Calcd for $C_9H_{15}SI$: C, 38.31; H, 5.36. Found: C, 38.46; H, 5.21.

Acknowledgment. We gratefully acknowledge Takeda Chemical Industries Ltd. for obtaining the mass spectral data.

Registry No.—**5**, 1073-76-3; **10a**, 67194-75-6; **10b**, 67194-76-7; **12**, 13334-79-7; **14**, 67194-77-8.

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Synthesis of Adamantane Derivatives. 42.[1] Novel Synthesis of 5-Methylene-4-azahomoadamantane Derivatives from 2-Methyl-2-hydroxyadamantane and Their Carbon-13 Nuclear Magnetic Resonance Spectra

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5-Methyl-4-azahomoadamant-4-ene (**9**), readily obtainable from 2-methyl-2-hydroxyadamantane (**8**), was converted to 4-acyl-5-methylene-4-azahomoadamantanes **11a**, **11b**, and **11c** in good yields on acylation. The reaction of **9** with dichlorocarbene gave also 4-formyl-5-methylene-4-azahomoadamantane (**16**), while peracetic acid oxidation of **9** gave the corresponding oxaziridine **17**. 4,5-Dimethyl-4-azahomoadamantenium iodide (**18a**), the methiodide of **9**, gave 4-methyl-5-methylene-4-azahomoadamantane (**19**) on treatment with aqueous alkali. ^{13}C NMR data of the thus prepared 5-methylene-4-azahomoadamantane derivatives have been reported.

4-Azahomoadamantane derivatives are known as potentially biologically active compounds,[2] and several synthetic routes to this skeleton have been reported recently by many workers. The Beckmann rearrangement[3] and the Schmidt reaction[4] of the adamantanone system (**1**) are the simple routes to 4-azahomoadamantan-5-one (**2**), but these reactions are prone to suffer from side reactions such as fragmentations. The rearrangement of spirooxaziridine (**3**) is known also as a direct route to *N*-alkyl-4-azahomoadamantan-5-one (**2**).[5] On the other hand, rearrangements via 1-adamantylnitrenium ion type intermediates as in the **4** → **5**,[6] **6** → **5**,[7] and **7** → **5**[8] conversions are unique routes to 3-substituted 4-azahomoadamantanes. In this paper, we report a novel and facile synthesis of 5-methylene-4-azahomoadamantane derivatives via 5-methyl-4-azahomoadamant-4-ene (**9**) from 2-methyl-2-hydroxyadamantane (**8**).

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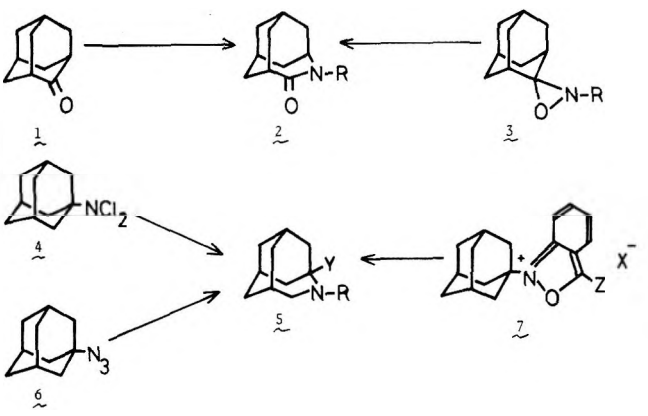
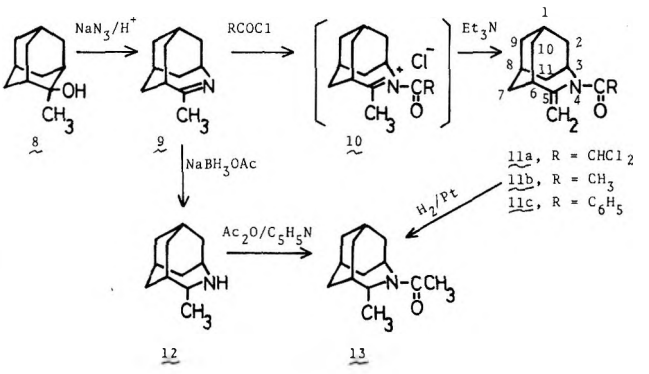
Table I. Chemical Shifts (δ) of 5-Methylene-4-azahomoadamantane Derivatives[a]

compd	$C_{1,8}$	$C_{2,11}$[b]	C_3	C_5	$=CH_2$	C_6	$C_{7,10}$[b]	C_9	C=O	other carbons
11a	26.4 (d)	33.6 (t)	49.9 (d)	153.3 (s)	108.0 (t)	37.6 (d)	36.3 (t)	35.1 (t)	163.3 (s)	64.1 (d)[c]
11b	26.7 (d)	34.2 (t)	48.3 (d)	153.6 (s)	107.4 (t)	38.1 (d)	36.6 (t)	35.4 (t)	169.5 (s)	23.8 (q)[d]
11c	26.6 (d)	34.6 (t)	48.2 (d)	152.2 (s)	109.5 (t)	37.8 (d)	36.7 (t)	35.3 (t)	169.3 (s)	138.2 (s) ($C_{1'}$)[e]
										128.9 (d) ($C_{4'}$)[e]
										127.7 (d) ($C_{2',3',5',6'}$)[e]
16	26.4 (d)	34.8 (t)[f]	46.5 (d)	153.2 (s)	98.2 (t)	38.2 (d)	36.2 (t)	34.8 (t)[f]	160.7 (s)	
19	26.3 (d)	36.4 (t)[f]	59.4 (d)	160.8 (s)	76.3 (t)	42.0 (d)	36.4 (t)[f]	35.2 (t)		40.4 (q)[g]

[a] Downfield from internal tetramethylsilane in $CDCl_3$, and see the structural formula for numbering of the carbon atoms. [b] See ref 13c. [c] $CHCl_2$. [d] CH_3. [e] Phenyl carbons. [f] Overlapped. [g] CH_3.



Scheme I



Results and Discussion

We have recently reported in a communication[9] that 2-alkyl-2-hydroxyadamantane can be converted in good yields to the corresponding 5-alkyl-4-azahomoadamant-4-ene by treatment with sodium azide in methanesulfonic acid. Thus, 5-methyl-4-azahomoadamant-4-ene (**9**) was obtained directly from 2-methyl-2-hydroxyadamantane (**8**)[10] in 79% yield simply by stirring **8** with a 4-fold excess of sodium azide in CH_3SO_3H–CH_2Cl_2, followed by the usual workup and distillation under reduced pressure. The imine **9** gave the corresponding hydrochloride with hydrogen chloride gas,[9] which was reconverted to free imine **9** with aqueous potassium hydroxide, indicating the considerable stability of **9** toward acid or base.

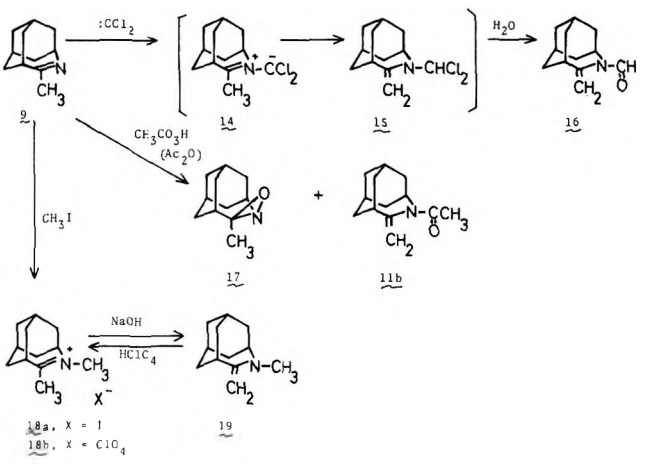
The additions of carbene and ketene to C=N double bonds are well known as simple routes to aziridines and azetidinones, respectively.[11,12] In order to examine the reactivity of the C=N double bond in **9**, **9** was treated with dichloroacetyl chloride in refluxing benzene containing triethylamine (the conditions for generation of dichloroketene) for 6 h. The usual workup and chromatography on an alumina column afforded an adduct **11a** in 55% yield as colorless crystals. This compound was not a dichloroketene adduct but was characterized as 4-dichloroacetyl-5-methylene-4-azahomoadamantane on the basis of analysis and spectral data. The IR (KBr) spectrum had strong absorptions at 1670 ($\nu_{C=O}$) and 1630 and 880 ($\nu_{C=CH_2}$) cm^{-1}. The ^1H NMR ($CDCl_3$) spectrum revealed signals at δ 6.90 (s, 1 H, $CHCl_2$), 5.00 and 4.82 (both s, each 1 H, $C=CH_2$), 4.77 (broad s, 1 H, C_3H), 3.00 (broad s, 1 H, C_6H), and 2.2–1.4 (m, 12 H, other protons), supporting the assigned structure of **11a** (Scheme I). Furthermore, the ^{13}C NMR spectrum had ten lines (Table I), which were compatible with the given structure. The assignments (Table I) were based on the chemical shifts, peak intensities, and proton off-resonance spectral data.[13]

Treatment of **9** with acetyl chloride and benzoyl chloride in the presence of triethylamine also gave the corresponding 4-acyl-5-methylene-4-azahomoadamantanes **11b** and **11c** in 66 and 82% yields, respectively. The structures of **11b** and **11c** were supported by the spectral data (see Experimental Section and Table I). Furthermore, **11b** was converted to 4-acetyl-5-methyl-4-azahomoadamantane (**13**) quantitatively on catalytic hydrogenation. The structure of **13** was confirmed by an alternative preparation via 5-methyl-4-azahomoadamantane (**12**), which is readily obtainable from **9** as shown in Scheme I.

The yields of dichlorocarbene addition to C=N double bonds have been much improved recently by applying the phase-transfer technique.[14] Therefore, **9** was treated with dichlorocarbene generated from chloroform and 50% aqueous potassium hydroxide under the phase-transfer catalyzed conditions using benzyltriethylammonium chloride (BTAC) as a catalyst. The product obtained in 66% yield as an oil after chromatography was shown by spectral data to be 4-formyl-5-methylene-4-azahomoadamantane (**16**). The formation of **16** can be rationalized by the initial formation of N–C ylide **14**, followed by proton loss or H migration and hydrolysis of the N–$CHCl_2$ group as depicted in Scheme II.[15]

Oxidation of **9** with peracetic acid prepared in situ from 35% hydrogen peroxide, acetic anhydride, and sulfuric acid by the Emmons' procedure[16] gave oxaziridine **17**, mp 65–68 °C, and **11b** in 23 and 9.4% yields, respectively (Scheme II). The as-

Scheme II



signed structure of **17** was supported by analysis and spectral data. The formation of **11b** as the minor product is ascribable to the reaction of **9** with acetic anhydride. This was independently proven through the preparation of **11b** by treating **9** with acetic anhydride and sulfuric acid.

All of the above results indicate that the iminium salt of **9** can be converted to 4-acyl-5-methylene-4-azahomoadamantane derivatives. Furthermore, an example of enamine formation from bicyclic *N*-methyliminium iodide has been reported previously by Walker and Alkalay.[17a] Therefore, the 4-alkyliminium salt of **9** may be a promising precursor to 4-alkyl-5-methylene-4-azahomoadamantane. In fact, the reaction of aqueous sodium hydroxide with 4-methyliminium iodide **18a**, which was readily obtained from **9** and methyl iodide, afforded 4-methyl-5-methylene-4-azahomoadamantane (**19**) in 80% yield.[17b] The structure of **19** was supported by analysis and spectral data. The IR (film) spectrum had a strong absorption at 1600 cm^{-1}, and the ^1H NMR ($CDCl_3$) spectrum revealed signals at δ 3.7–2.95 (broad m, 3 H, C=CH_2 and C_3 H), 2.82 (s, 3 H, CH_3), 3.0–3.3 (broad m, 1 H, C_6 H), and 2.2–1.4 (m, 12 H, other protons). The appearance of the vinylic protons at characteristically higher field supported the assigned enamine structure **19**. In the ^{13}C NMR spectrum (Table I), one of the vinylic carbons (=CH_2) appeared also at considerably higher field (δ 76.3). The enamine **19** was converted to 4,5-dimethyl-4-azahomoadamant-4-enium perchlorate (**18b**) on treatment with perchloric acid (Scheme II).

Because 2-alkyl-2-hydroxyadamantanes such as **8** are readily obtainable from adamantanone and Grignard reagents or alkyllithium, the above facile formation of 4-acyl- and 4-alkyl-5-methylene-4-azahomoadamantanes via **9** may provide a novel and convenient route to 5-alkylidene-4-azahomoadamantane derivatives from adamantanone.

Experimental Section[18]

5-Methyl-4-azahomoadamant-4-ene (9). To a stirred and ice-cooled mixture of 98% methanesulfonic acid (15 mL) and dichloromethane (10 mL) was added solid sodium azide (0.52 g, 8.0 mmol) and then 2-methyl-2-hydroxyadamantane (**8**)[10] (1.00 g, 6.00 mmol). To the resulting mixture was added little by little sodium azide (1.04 g, 16.0 mmol) during 0.5 h. After the stirring was continued further for 8 h at 20–25 °C, the mixture was poured onto ice water (ca. 10 mL). The aqueous layer was separated, washed with CH_2Cl_2 (3 mL), basified with 50% aqueous KOH–ice, and extracted with CH_2Cl_2 (10 mL × 4). The combined extracts were dried (Na_2SO_4), and the solvent was removed to afford a brownish oil which was purified by Kugelrohr distillation (120 °C, 0.2 mm) to give **9** as a colorless oil (0.77 g, 79%): $n^{22}D$ 1.5155; IR (film) 2920, 2850, 1660, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (t, J = 4.0 Hz, 1 H, C_3 H), 2.57 (t, J = 4.0 Hz, 1 H, C_6 H), 2.00 (s, 3 H, CH_3), and 1.9–1.5 (m, 12 H).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 81.20; H, 10.33; N, 8.47.

The hydrochloride of **9** was obtained on treatment with HCl gas in ether as a colorless precipitate, mp 278–280 °C dec.[9]

4-Dichloroacetyl-5-methylene-4-azahomoadamantane (11a). To a stirred and refluxing mixture of **9** (81 mg, 0.50 mmol) and triethylamine (101 mg, 1.00 mmol) in anhydrous benzene (6 mL) was added dichloroacetyl chloride (147 mg, 1.00 mmol) in benzene (3 mL) during 0.5 h under an argon atmosphere. After the refluxing was continued further for 6 h, the cooled mixture was washed with water and dried (Na_2SO_4). Removal of the solvent gave a brownish oil which was purified on an alumina column (Wako, basic, grade I) eluting with CH_2Cl_2 to afford **11a** as colorless crystals (76 mg, 55.4%): mp 61–63 °C (*n*-hexane); IR (KBr) 3040, 2920, 2850, 1670, 1630, 1450, 1405, 1190, and 880 cm^{-1}; ^1H and ^{13}C NMR, see text and Table I.

Anal. Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11. Found: C, 56.93; H, 6.10; N, 5.26.

The same reaction at −78 °C for 15 h and at 20–25 °C for 9 h in anhydrous ether as the solvent also gave **11a** in 55.3 and 54.3% yields, respectively.

4-Acetyl-5-methylene-4-azahomoadamantane (11b). A mixture of **9** (81 mg, 0.50 mmol) and triethylamine (76 mg, 0.75 mmol) in ether (3 mL) was treated with acetyl chloride (59 mg, 0.75 mmol) in ether (2 mL) at 20–25 °C for 1 day. Removal of the solvent gave the crude product, which was purified on an alumina column eluting with CH_2Cl_2 to afford **11b** as colorless crystals (68 mg, 66%): mp 37–40 °C (*n*-hexane); IR (KBr) 3120, 2920, 2850, 1640, 1630, 1450, 1395, 1320, and 870 cm^{-1}; ^1H NMR ($CHCl_3$) δ 4.90 (s, 1 H), 4.80 (broad s, 1 H), 4.60 (s, 1 H), 2.90 (broad s, 1 H), 2.20 (s, 3 H), and 2.1–1.3 (m, 12 H); ^{13}C NMR ($CDCl_3$), see Table I.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.36; H, 9.17; N, 6.91.

4-Benzoyl-5-methylene-4-azahomoadamantane (11c). A mixture of **9** (81 mg, 0.50 mmol) and triethylamine (76 mg, 0.75 mmol) in anhydrous ether (3 mL) was treated with benzoyl chloride (106 mg, 0.75 mmol) in ether (2 mL) as above for 2 h at 20–25 °C. Workup as above and chromatography on an alumina column eluting with CH_2Cl_2 afforded **11c** as colorless crystals (110 mg, 82.3%): mp 122–125 °C; IR (KBr) 3060, 2920, 2840, 1620, 1580, 1450, 1395, 1335, 870, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.1 (m, 5 H), 5.10 (broad s, 1 H), 4.52 (s, 1 H), 4.07 (s, 1 H), 2.90 (broad s, 1 H), and 2.3–1.5 (m, 12 H); ^{13}C NMR ($CDCl_3$), see Table I.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.86; H, 7.79; N, 5.37.

5-Methyl-4-azahomoadamantane (12). To a solution of **9** (50 mg, 0.31 mmol) in anhydrous dioxane (5 mL) was added sodium acetoxyborohydride[19] (294 mg, 3.00 mmol), and the mixture was heated under reflux for 7 h. The cooled mixture was diluted with water (20 mL) and extracted with chloroform (9 mL × 4). The combined extracts were washed with saturated aqueous sodium chloride solution, dried (Na_2SO_4), and concentrated to ca. 15 mL, which was diluted with ether (10 mL) and treated with HCl gas. Removal of the solvent gave a solid which was reprecipitated from CH_2Cl_2–*n*-hexane to afford the hydrochloride of **12** (29 mg, 46%): mp 295–298 °C dec; IR (KBr) 3200–2400 and 1585 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 4.0–3.3 (m, 12 H), 2.66–1.3 (m, 13 H), and 1.53 (d, J = 7.0 Hz, 3 H).

Anal. Calcd for $C_{11}H_{20}NCl$: C, 65.49; H, 9.92; N, 6.92. Found: C, 65.58; H, 9.87; N, 6.88.

4-Acetyl-5-methyl-4-azahomoadamantane (13). A. From 11b. A mixture of **11b** (22 mg, 0.11 mmol) and Adams' catalyst (22 mg) in methanol was stirred under a hydrogen atmosphere for 48 h at room temperature. Removal of the catalyst by filtration and removal of the solvent gave **13** as colorless crystals (22 mg, 99%): mp 35–39 °C; IR (KBr) 2920, 2850, 1630, 1440, 1080, and 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.37–3.64 (m, 2 H), 2.20 and 2.14 (each s, 0.86 H and 2.14 H), 2.5–1.0 (m, 13 H), and 1.34 and 1.23 (each d, J = 6.7 Hz, 0.86 H and 2.14 H).[20]

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.58; H, 9.98; N, 6.73.

B. From 12. A mixture of the hydrochloride of **12** (10 mg, 0.050 mmol) and acetic anhydride (108 mg, 1.1 mmol) in pyridine (0.5 mL) was stirred for 1 day at room temperature. The usual workup with sublimation gave **13** as a colorless solid (10 mg, 100%) which had the same IR and ^1H NMR spectra as the sample prepared from **11b**.

4-Formyl-5-methylene-4-azahomoadamantane (16). To a vigorously stirred mixture of **9** (160 mg, 1.0 mmol), benzyltriethylammonium chloride (7 mg), 50% aqueous KOH (2 mL), and benzene (2 mL) was added a mixture of chloroform (1.2 g, 10 mmol) and benzene (2 mL) during 1 h at room temperature, and the stirring was continued further for 6 h. The mixture was diluted with water (10 mL) and extracted with ether (6 mL × 3). The combined extracts were dried (Na_2SO_4). Removal of the solvent gave a brownish oil which was purified on an alumina column eluting with *n*-hexane–CH_2Cl_2 to afford **16** as a colorless oil (122 mg, 65.9%): $n^{19.5}D$ 1.5510; IR (film) 3100, 2920, 2850, 1660, 1620, 1440, 1380, 1270, and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.47 (s, 1 H, CHO), 4.67 (broad s, 1 H, C_3 H), 4.48 and 4.52 (each s, 2 H, C=CH_2), 2.85 (broad s, 1 H, C_6H), and 2.4–1.3 (m, 12 H); ^{13}C NMR ($CDCl_3$), see Table I.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 8.93; N, 7.33.

3′-Methyl-4-azahomoadamantano[4,5-*b*]oxaziridine (17). To a stirred and ice-cooled mixture of 35% aqueous H_2O_2 (0.08 mL, 0.82 mmol) and dichloromethane (2 mL) was added successively 97% H_2SO_4 (0.03 mL) and acetic anhydride (65 mg, 0.63 mmol), and the mixture was stirred for 15 min under ice cooling and 5 min at 20 °C. This peracetic acid solution was added to a stirred and ice-cooled solution of **9** (81 mg, 0.50 mmol) in CH_2Cl_2 (2 mL), and the stirring was continued for 15 h at 20–25 °C. The mixture was treated with 5% aqueous sodium thiosulfate and dried (Na_2SO_4). Removal of the solvent gave an oil which was purified by preparative TLC (alumina, CH_2Cl_2) to afford **11b** (10 mg, 9.7%) and **17** as colorless crystals (21 mg, 23%): mp 65–68 °C; IR (KBr) 3000, 2900, 2850, 1440, 1380, 1180, 1110, and 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (broad s, 1 H, C_3H), 2.35 (broad s, 1 H, C_6 H), 2.2–1.5 (m, 12 H), and 1.47 (s, 3 H, CH_3).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C,

73.78; H, 9.42; N, 7.70.

The acetyl derivative **11b** was identified by comparison of its IR spectrum and R_f values on TLC with the sample prepared from **9** and acetyl chloride. Treatment of **9** with acetic anhydride in CH_2Cl_2 in the presence of a catalytic amount of sulfuric acid also gave **11b** (37%).

4,5-Dimethyl-4-azahomoadamant-4-enium Iodide (18a). A mixture of **9** (81 mg, 0.50 mmol) and methyl iodide (1.14 g, 8.0 mmol) in chloroform (3 mL) was heated under reflux for 1 day. Removal of the solvent and excess methyl iodide gave a brownish solid which was washed with acetone to afford **18a** as a colorless solid (130 mg, 85.5%): mp 277–280 °C dec; IR (KBr) 2920, 2850, 1660, 1450, and 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (broad s, 1 H), 3.90 (s, 3 H), 3.19 (broad s, 1 H), 2.87 (s, 3 H), and 2.55–1.81 (m, 12 H).

Anal. Calcd for $C_{12}H_{20}NI$: C, 47.23; H, 6.61; N, 4.59. Found: C, 47.22; H, 6.32; N, 4.62.

The methiodide **18a** was also obtained in 65.5% overall yield from **8** (450 mg, 2.70 mmol) without isolation of **9** by the same procedure.

4-Methyl-5-methylene-4-azahomoadamantane (19) and 4,5-Dimethyl-4-azahomoadamant-4-enium Perchlorate (18b). A solution of **18a** (305 mg, 1.00 mmol) in methanol (10 mL) was poured onto ice-cooled 10% aqueous NaOH (60 mL), and the mixture was extracted with ether (15 mL × 4). The combined extracts were dried (Na_2SO_4–K_2CO_3), and removal of the solvent gave an oil which was purified by Kugelrohr distillation (120 °C, 0.2 mm) to afford the enamine **19** as a colorless oil (142 mg, 80.0%). **19** turned to a yellowish oil rapidly in the air: $n^{19}D$ 1.5487; IR (film) 3120, 2920, 2840, 1600, 1440, 1400, 1300, 1030, and 750 cm^{-1}; ^1H and ^{13}C NMR, see text and Table I.

Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.50; H, 10.57; N, 7.93.

To a solution of **19** (78 mg, 0.44 mmol) in methanol (2 mL) and ether (10 mL) was added 70% aqueous perchloric acid (0.1 mL) to afford a colorless precipitate which was filtered off and washed with ether to give **18b** (122 mg, 100%): mp >300 °C; IR (KBr) 2920, 2870, 1667, 1450, and 1090 cm^{-1}; ^1H NMR [$CDCl_3$–D_2O–$(CD_3)_2SO$] δ 4.18 (broad s, 1 H), 3.70 (s, 3 H), 3.22 (s, 3 H), 3.4–3.0 (broad m, 1 H), and 2.75–1.50 (m, 12 H).

Anal. Calcd for $C_{12}H_{20}NO_4Cl$: C, 51.89; H, 7.26; N, 5.04. Found: C, 52.12; H, 7.01; N, 4.93.

Registry No.—**8**, 702-98-7; **9**, 65218-97-5; **11a**, 67180-43-2; **11b**, 67180-44-3; **11c**, 67180-45-4; **12** HCl, 65219-01-4; **13**, 67180-48-7; **16**, 67180-46-5; **17**, 67180-49-8; **18a**, 67180-50-1; **18b**, 67180-52-3; **19**, 67180-47-6; dichloroacetyl chloride, 79-36-7; acetyl chloride, 75-36-5; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7.

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Methano-Bridged 10π-Electron Aromatic Annulenes. 4-Methoxy-1,6-methanoisoquinoline

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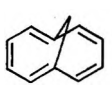
The synthesis of 4-methoxy-1,6-methanoisoquinoline (**2b**), a 10π-electron heterocyclic methano-bridged system, is described. The ring skeleton is generated via a Beckmann rearrangement of tricyclo[4.3.1.$0^{1,6}$]-2,4-decadien-8-one oxime (**3**). Aromatization of the resulting lactam is accomplished by introduction of a methylthio group, its oxidation to a sulfone, amide *O*-methylation, and elimination of methanesulfinic acid. Compound **2b** shows ^1H NMR chemical shifts indicative of a 10π-electron delocalized system.

There have been several examples of aromatic 10π- and 14π-electron methano-bridged systems since the synthesis of 1,6-methano[10]annulene[1] (**1**) but very few have been heterocyclic in nature.[2] Our present concern is with methano-bridged counterparts of indole, quinoline, isoquinoline, carbazole, and similar species from the viewpoint of aromaticity studies and modification of physiological activity in drugs containing such skeletons.



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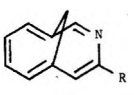

2 (a, R = H; b, R = OCH_3)

The skeletal unit of interest in this work is 1,6-methanoisoquinoline (**2a**), and the synthesis of one of its derivatives, 4-methoxy-1,6-methanoisoquinoline (**2b**) is described.

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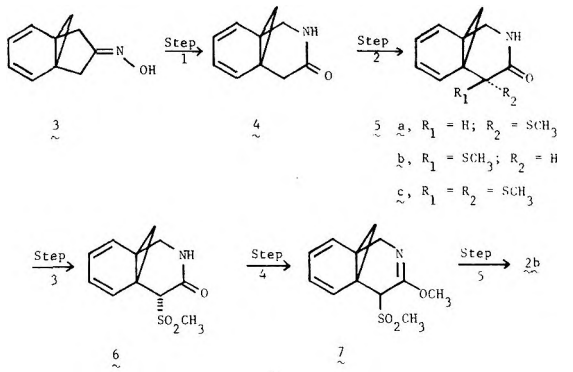
Scheme I



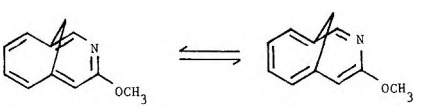
Entry into the 1,6-methanoisoquinoline skeleton (Scheme I) was accomplished via the known oxime of tricyclo[4.3.1.0^{1,6}]-2,4-decadien-8-one[7] (**3**). The sequence involved ring expansion (step 1), substitution (step 2), sulfur oxidation (step 3), *O*-alkylation (step 4), and elimination (step 5).

Two aspects of the structure of **2b** are indicated by its ^{1}H NMR spectrum. The methylene protons at δ −0.05 (d, J = 9.5 Hz) and 0.45 (dd, J = 9.5 Hz, J' = 1.8 Hz) indicate an open-ring structure because of the magnitude of the geminal coupling constant ($J_{cyclopropane} \approx 5$ Hz). Also, chemical shifts reflect the presence of a diamagnetic ring current, for they span a region between aromatic and vinyl protons (δ 5.94–7.44 for the protons on sp^2 carbons). Finally, the constancy of the ^{1}H NMR spectrum with temperature suggests that there is no bond equilibration between potential structures **2b** and **2b'**, in accord with what might be expected from reported conjugational relationships involving reactions of methyl imidate functionalities.[8]

Discussion

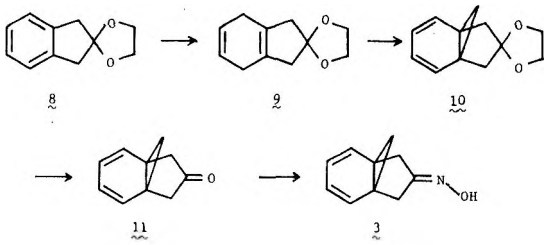
The typical synthetic route to a number of methano-bridged systems utilized a procedure of Birch reduction of the parent aromatic system, cyclopropanation of the tetrasubstituted double bond, and rearomatization directly (oxidative dehydrogenation) or indirectly (substitution–elimination). Such was the case in the conversion of naphthalene to **1**.[1] This type of procedure was not applicable to the preparation of a methano-bridged isoquinoline because Birch reduction of isoquinoline leads to 1,2,3,4-tetrahydroisoquinoline only.[9] Although further reduction might provide a tetrasubstituted double bond, considerable problems were expected from the saturated heterocyclic ring.

These problems led to the consideration of oxime **3** as a target for entry into the 1,6-methanoisoquinoline skeleton, for a Beckmann rearrangement of **3** or one of its derivatives would lead to the correct placement of nitrogen in the ring skeleton. Further transformations would lead to either **2a** or **2b**.



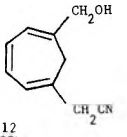
The synthesis of oxime **3** (Scheme II) was carried out with rather extensive modifications of the procedure employed by Vogel.[7] The ethylene ketal of 2-indanone[10] (**8**) was reduced by lithium and isopropyl alcohol in liquid ammonia to 4,7-dihydro-2-indanone ethylene ketal (**9**) in 84% yield. Instead of cyclopropanation via a dichlorocarbene, better yields were obtained with the Simmons–Smith reagent. The nucleophilic tetrasubstituted double bond was expected to show more selectivity toward the reagent, and the ketal oxygens would provide an added directive effect.[11] In this manner, when **9** was treated with a Zn–Cu couple[12] and methylene iodide at

Scheme II

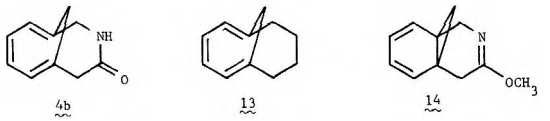


45 °C for 24 h, approximately 50% of cyclopropanation resulted. Longer reaction times usually led to resinification. Such problems were circumvented by the use of a Zn–Ag couple,[13] so that cyclopropanation was complete after 3 h at 45 °C with a yield of 70% of **10**. In this way, no exo or bis product was detectable by ^{1}H NMR. The remainder of the conversion was essentially that described by Vogel,[7] without isolation and characterization of the dibromide addition intermediate or purification of the diene ketal.

Initial attempts to employ acidic conditions for the Beckmann rearrangement of **3** to **4** resulted in very low lactam yields and/or extensive decomposition of the starting material. Solvolytic rearrangement to **4** proceeded in 60% yield when the benzenesulfonate ester of oxime **3** was refluxed with aqueous tetrahydrofuran. The abnormal Beckmann rearrangement product, nitrile alcohol **12** (22% yield), as well as diene ketone **11** (12% yield) were obtained as side products of the reaction.

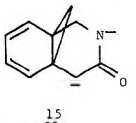


It is interesting to note that the proton geminal coupling constant of the methylene bridge (J = 4.5 Hz) indicated that lactam **4** exists as the norcaradiene rather than the cycloheptatriene (**4b**), even though earlier work[14] had shown that the latter was the preferred form for a hydrocarbon ring system (**13**) of the same size.



Lactam **4** can be considered to be a dihydromethano-bridged aromatic species. This is more clearly shown for its imino ether, **14**, which was made in 94% yield by alkylating **4** with trimethyloxonium fluorborate in the presence of potassium carbonate. Even though **4** and **14** were oxidatively close to the fully aromatic product, no apparent aromatization occurred with reagents such as chloranil, dichlorocyanoquinone, palladium on charcoal, platinum black, trityl fluoroborate, selenium, manganese dioxide, or *N*-lithioethylenediamine. It was clear that a less direct dehydrogenation was needed.

Generation of intermediates suitable for elimination reactions through a monoanion of **4** was also unproductive, but the dianion of **4** showed promise of practicality. Thus, when **4** was treated with an excess of lithiodiisopropylamide or *n*-butyllithium, dianion **15** was formed.



Quenching of **15** with bromine led to extensive decomposition of starting material. The use of disulfides, as described by Trost[15] for quenching enolates of esters and ketones, pro-

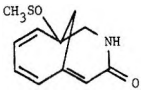
duced stable species that proved to be practical for later elimination. Significant time and concentration dependencies were noted for this reaction, and it was observed that dimethyl disulfide but not diphenyl disulfide was an effective sulfenylating agent.

Operationally, the generation of **15** was best accomplished by adding butyllithium to a stirred solution containing **4**, diisopropylamine, and hexamethylphosphoramide (HMPA) in tetrahydrofuran at 0 °C. The solution of the dianion thus formed was usable for at least 30 min if kept at that temperature. If the ratio of base to lactam was greater than 2.0, the bis-sulfenylated lactam **5c** predominated. As the ratio was decreased to about 1.7, larger amounts of monosulfenylated products **5a** and **5b** were produced. Below 1.7, unreacted starting material became dominant. Dimethyl disulfide was added 5 min after the addition of the base. This sulfenylation reaction was allowed to proceed for 30 min because longer reaction times led to greater quantities of starting lactam and **5c**, apparently via a disproportionation reaction.

The mixture of stereoisomeric, monosulfenylated lactams **5a** and **5b** were difficulty separable, but it was found that isomerization to **5a** only occurred by treatment with potassium carbonate in methanol. No attempt was made to characterize the stereochemical structure of **5a** because later reactions were expected to destroy the isomeric integrity at this position. However, it might reasonably be assumed that the methylthio group is anti to the cyclopropane ring because of steric preference.

Aromatization processes considered for **5a** and/or **5b** involved a sulfonium salt, sulfoxide, or sulfone (**6**). For the first, alkylations of **5a,b** or **5a** only were attempted under a number of conditions with excess trimethyloxonium fluoroborate. The only product isolated was an imino ether.

The sulfoxide had some interesting prospects as an intermediate, particularly as an origin for a 2,3-sigmatropic shift to a sulfenate[16] (**16**). The sulfoxide could be prepared in nearly quantitative yield by oxidation of **5a** with *m*-chloroperbenzoic acid at −78 °C. Attempted rearrangement–hydrolysis reactions produced only starting material or decomposition products.



16

The sulfone **6** could be made nearly quantitatively from **5a**, and methylation to **7** (50:50 mixture of isomers) occurred in 96% yield. Since basic conditions were to be used for the next reaction, separation of the stereoisomers of **7** was not attempted. In that last step, **2b** was isolated in 21% yield from the reaction of **7** with potassium *tert*-butoxide at 80 °C.

The chemical shifts of vinyl and aromatic protons in methano-bridged compounds are essentially the same as those seen for conventional species. In **2b** they fall into the range that indicates aromaticity. The bridge protons, however, show evidence of a weaker ring current than in the carbocyclic species, 1,6-methano[10]annulene.

Experimental Section

Tetrahydrofuran (THF) was purified by distillation from potassium benzophenone ketyl, and other solvents were distilled prior to use. The ^{1}H NMR spectra were recorded on one or more of the following instruments: Varian A-60D, Varian EM-390, Brüker WH-90 Multinuclear, or Varian HR-220 (for compound **2b**). Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer, ultraviolet spectra from a Carey 14 spectrophotometer, low-resolution mass spectra from a Finnegan 1015 S/L spectrometer, and high-resolution mass spectra from an ARI-MS9 spectrometer (the last at the University of California, Los Angeles). Microanalyses were performed by C. F. Geiger, Ontario, Calif. Melting points are uncorrected.

4,7-Dihydro-2-indanone Ethylene Ketal (9). A solution of 19.7 g (0.112 mol) of 2-indanone ethylene ketal (**8**) in 50 mL of anhydrous ether was added to 200 mL of liquid ammonia at −78 °C. Over a 4-h period lithium wire in 4-cm portions and 2-propanol in 2-mL portions were added, so that a total of 50 cm (2.0 g, 0.29 g-atoms) of the former and 24 mL (18.8 g, 0.31 mol) of the latter were introduced. After 2 h the temperature was allowed to rise to that of refluxing ammonia and kept there for 5 h. After ammonia was allowed to evaporate, water was added and the aqueous layer was extracted three times with ether. The combined organic layers were washed twice with water and once with saturated NaCl, dried with magnesium sulfate, and concentrated by evaporation to yield 15.6 g of a nearly white solid. Crystallization from low-boiling petroleum ether gave **9** (15.0 g, 84% yield) as a white solid, mp 44–45 °C (lit.,[10] 43–44 °C).

Tricyclo[4.3.1.0^{1,6}]-2,4-decadien-8-one Ethylene Ketal (10). The methylene bridge was introduced into **9** using methylene iodide and the zinc–silver couple as described by Denis et al.[13] A mixture of the couple (prepared from 23.8 g of zinc and 130 mg of silver acetate), 25.8 g (0.145 mol) of ketal **9** in 60 mL of ether, and 300 mg (2.80 mg-atoms) of silver dust (as opposed to silver wool) was prepared, and 50.5 g (0.189 mol) of methylene iodide was added at such a rate to maintain gentle reflux. Refluxing was maintained for 3 h after complete addition, then the mixture was cooled, and an equal volume of ether was added. Pyridine was added in two portions, followed by filtration after each addition to remove the inorganic precipitate. Concentration of the filtrate by evaporation yielded 25.5 g of a brown oil. Distillation (62–65 °C at 0.05 mmHg) gave 19.4 g (70%) of **10** as a clear oil: ^{1}H NMR (CCl_4, Me_4Si) δ 0.45 (d, 1, J = 4 Hz, cyclopropyl H anti to ketal), 0.70 (d, 1, J = 4 Hz, cyclopropyl H syn to ketal), 1.94 (s, 4, methylene H of 5-membered ring), 2.22 (m, 4, allylic H), 3.76 (m, 4, ketal H), 5.46 (m, 2, olefinic H).

Tricyclo[4.3.1.0^{1,6}]-2,4-decadien-8-one (11). Ketal **10** (17.5 g, 0.092 mol) in 75 mL of dichloromethane was cooled to −78 °C under nitrogen. Bromine (14.7 g, 0.092 mol) was added dropwise to the stirred solution. After 30 min, excess sodium bisulfite and 10 mL of absolute methanol were added and the mixture was warmed to 0 °C. After filtration and removal of the solvent at 0 °C, the resulting solid was transferred to a hot solution of sodium ethoxide (0.46 mol) in 250 mL of ethanol. The mixture was refluxed for 2 h with stirring, cooled, diluted with water, and extracted five times with pentane. The combined organic phases were washed twice with water, dried over magnesium sulfate, and concentrated to yield the crude diene ketal. A solution of the ketal in 200 mL of THF was refluxed for 2 h with 50 mL of 0.5 M HCl. After cooling, the mixture was neutralized with sodium bicarbonate and extracted three times with ether. The organic phases were washed successively with saturated sodium bicarbonate and saturated sodium chloride and then dried over magnesium sulfate. After removal of the solvent, the product was crystallized from ether to give 7.8 g (59%) of **11** as a white solid: mp 98–100 °C (lit.[7] 99–100 °C).

Tricyclo[4.3.1.0^{1,6}]-2,4-decadien-8-one Oxime (3). The oxime was prepared in 97% yield. Recrystallization did not significantly alter the product: mp 76–78 °C (lit.,[7] 77–78 °C).

Beckmann Rearrangement of Oxime 3. Oxime **3** (7.33 g, 45.5 mmol) in 200 mL of THF was cooled to 0 °C under a nitrogen atmosphere. Then, 23 mL of 2 M sodium hydroxide was added, followed by the dropwise addition of benzenesulfonyl chloride (8.05 g, 45.5 mmol). After the mixture was stirred at 0 °C for 30 min, 200 mL of water was added and the resulting solution was refluxed for 3.5 h. The cooled reaction mixture was poured into dichloromethane and the organic layer was combined with three dichloromethane washings of the aqueous phase. The combined organic phases were washed with saturated sodium chloride, dried over magnesium sulfate, and concentrated, to yield 6.75 g of a tan solid. The product was chromatographed on silica gel with elution by dichloromethane to yield 779 mg (12%) of the diene ketone **11**. Subsequent elution with 2% ethyl acetate/dichloromethane gave 1.57 g (21%) of a yellow oil whose ^{1}H NMR and infrared spectra were consistent with those expected of the abnormal Beckmann product, **12**. Nitrile alcohol **12** was purified and characterized as the phenylurethane: mp 115 °C. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.38; H, 5.89; N, 10.37.

Final elution of the silica gel column with 10% ethyl acetate/dichloromethane gave 4.40 g (60%) of lactam **4** as a white solid: mp 127 °C; ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ −0.13 (dd, 1, J = 4.5 Hz, J' = 1.5 Hz), 1.71 (d, 1, J = 4.5 Hz), 2.50 (dd, 1, J = 16.5 Hz, J' = 1.5 Hz), 2.90 (d, 1, J = 16.5 Hz), 3.46 (d, 1, J = 13.0 Hz), 3.70 (dd, 1, J = 13.0 Hz, J' = 5.0 Hz; the latter shown by decoupling to be coupled to the NH), 5.91 (s, 4), 6.40–6.71 (s, 1).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.77; H, 6.78; N, 8.60.

หอสมุดกลาง กรมวิทยาศาสตร์

Sulfenylation of Lactam 4. To a solution of lactam **4** (906 mg, 5.63 mmol) dissolved in 35 mL of anhydrous THF were added 1.08 g (10.7 mmol) of diisopropylamine and 1.92 g (10.7 mmol) of HMPA. The stirred solution was cooled to −15 °C under argon; then 9.52 mmol of butyllithium in hexane was added as quickly as possible without allowing the temperature to rise above 0 °C. Five minutes after the addition was complete, 616 mg (6.55 mmol) of dimethyl disulfide was added. The cooling bath was removed and after 30 min water was added. The reaction mixture was extracted three times with ether. The combined organic extracts were washed once with 3 M HCl, once with saturated sodium bicarbonate, and once with saturated sodium chloride. The solution was dried over magnesium sulfate, filtered, and concentrated to yield 952 mg of a yellow oil. Chromatography on silica gel and elution with 50% ether/dichloromethane yielded the bis(methylthiolactam) **5c** (184 mg, 13%) as a white solid. Continued elution gave the mono(methylthiolactams) **5a** and **5b** (402 mg, 34%) and finally lactam **4**, the last as an impure solid (20–30%).

Crystallization of **5c** gave a pure product: mp 187–188 °C; ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ 0.07 (d, 1, J = 5.0 Hz, cyclopropyl H syn to diene), 1.97 (d, 1, J = 5.0 Hz, cyclopropyl H anti to diene), 2.09 (s, 3, SCH_3), 2.23 (s, 3, SCH_3), 3.66 (d, 2, J = 6.0 Hz, methylene α to NH, shown by decoupling), 5.75–6.28 (m, 4, olefinic protons), 6.64–6.89 (m, 1, NH); IR (KBr) 3.02, 3.40, 5.98, 6.05, 6.80, 7.05, 7.65, 8.43, 9.20, 9.65, 9.80, 10.40, 11.10, 11.50, 12.00, 12.60, 13.50, 13.90, and 14.50 μm UV ($CHCl_3$) λ_{max} 280 nm, log ϵ 3.41.

Anal. Calcd for $C_{12}H_{15}NOS_2$: C, 56.88; H, 5.97; N, 5.53; S, 25.31. Found: C, 56.94; H, 5.84; N, 5.56; S, 24.98.

Mixture of **5a** and **5b**. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; S, 15.47. Found: C, 63.71; H, 5.93; S, 15.29.

Alternate Procedure for Sulfenylation of Lactam 4. Lithiodiisopropylamide was made by adding 11.5 mL (18.0 mmol) of 1.56 M butyllithium in hexane to a stirred solution of diisopropylamine (2.04 g, 20.2 mmol) in 10 mL of THF at 0 °C under argon. After 20 min, the resulting solution was added as quickly as possible to a stirred solution of lactam **4** (1.81 g, 11.2 mmol) of HMPA (3.62 g, 20.2 mmol) in 40 mL of THF at −10 °C. After 5 min, 1.08 g (11.5 mmol) of dimethyl disulfide was added at once and the cooling bath removed. Water was added after 30 min and the aqueous layer was extracted three times with ether. The combined organic extracts were washed once with 3 M HCl, once with saturated sodium bicarbonate, and once with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to yield 1.32 g of a yellow oil. Chromatography on silica gel and elution with 10% ethyl acetate/dichloromethane gave 589 mg (26%) of a mixture of methylthiolactams **5a** and **5b**. The bis product was not isolated.

***anti*-4-Aza-3-oxo-2-methylthiotricyclo[4.4.1.0^{1,6}]-7,9-undecadiene (5a).** To a solution of mixed methylthiolactams **5a** and **5b** (980 mg, 4.73 mmol) in 50 mL of absolute methanol was added 700 mg (5.06 mmol) of anhydrous potassium carbonate. The mixture was stirred under nitrogen for 48 h. Water was added and the aqueous layer was extracted three times with ether. The organic extracts were washed once with saturated sodium chloride, dried over magnesium sulfate, and concentrated to yield 823 mg (84%) of a white solid: mp 153–153.5 °C; ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ −0.07 (d, 1, J = 4.5 Hz, cyclopropyl H syn to diene), 1.84 (d, 1, J = 4.5 Hz, cyclopropyl H anti to diene), 2.15 (s, 3, SCH_3), 3.63 (d, 2, J = 6.0 Hz, methylene H α to NH as shown by decoupling), 3.80 (s, 1, methine H α to carbonyl), 5.62–6.25 (m, 5, olefinic H and NH); IR (KBr) 3.25, 3.38, 3.55, 6.00, 6.78, 7.10, 7.25, 7.45, 7.62, 7.88, 8.02, 8.38, 8.50, 8.60, 8.90, 9.10, 9.60, 9.80, 10.18, 10.28, 10.52, 11.02, 11.80, 12.24, 12.75, 13.71 and 14.50 μm.

Oxidation of Methylthiolactam 5a. Methylthiolactam **5a** (667 mg, 3.22 mmol) in 60 mL of dichloromethane was cooled to −78 °C under nitrogen. Then 1.31 g (6.5 mmol) of 85% *m*-chloroperbenzoic acid was added and the mixture was stirred at that temperature for 2 h. The solution was warmed to 0 °C and stirred for an additional 2 h. After neutralization with 5% potassium carbonate, the mixture was extracted three times with dichloromethane, which was dried over magnesium sulfate and concentrated to yield 769 mg (99%) of the sulfone lactam **6** as a white solid. A sample for analysis was crystallized from absolute ethanol: mp 192–194 °C; ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ 0.02 (d, 1, J = 5.0 Hz, cyclopropyl H syn to diene), 1.73 (d, 1, J = 5.0 Hz, cyclopropyl H anti to diene), 2.96 (s, 3, SO_2CH_3), 3.67 (dd, 1, J = 11.0 Hz, J' = 6.0 Hz, methylene H, the latter shown by decoupling to be due to NH), 3.84 (d, 1, J = 11.0 Hz, methylene H), 5.77–6.48 (m, 5, olefinic H and NH); IR (KBr) 3.20, 3.45, 3.55, 6.00, 6.12, 6.80, 7.24, 7.65, 8.40, 8.85, 9.12, 9.60, 9.75, 10.30, 11.04, 11.45, 12.20, 12.44 and 13.70 μm; UV (methanol) λ_{max} 272 nm, log ϵ 3.26.

High-resolution MS. Calcd for $C_{11}H_{13}NO_3S$: *m/e* 239.0615. Found: 239.0627.

Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.23; H, 5.68; N, 5.80; S, 13.22.

Sulfone Imino Ether 7. Anhydrous potassium carbonate (100 mg) was added to a stirred solution of the sulfone lactam **6** in 10 mL of dichloromethane under nitrogen at room temperature. Trimethyloxonium fluoroborate (197 mg, 1.33 mmol) was added and the mixture was stirred for 6 h. After the addition of water the mixture was extracted three times with dichloromethane, the organic layers were dried over magnesium sulfate, and the solvent was removed to yield 108 mg (96%) of the sulfone imino ether **7** as a 50:50 mixture of isomers (approximated from peak sizes in the ^{1}H NMR spectrum). The orange oil resisted further purification by chromatography or distillation: ^{1}H NMR for the mixed isomers ($CDCl_3$, $CHCl_3$) δ −0.02 and 0.24 (d, 1, J = 4.5 Hz, J = 5.0 Hz, cyclopropyl H syn to diene), 1.58 and 2.37 (d, 1, J = 4.5 Hz, J = 5.0 Hz, cyclopropyl H anti to diene), 2.80 and 3.30 (s, 3, SO_2CH_3), 3.73 (s, 3, OCH_3), 3.88–4.60 (m, 3, methylene and methine), 5.90–6.23 (m, 3, vinyl), 6.30–6.60 (m, 1, vinyl); IR (thin film) 3.30, 3.40, 3.50, 6.00, 7.00, 7.55, 7.68, 7.98, 8.08, 8.84, 9.88, 10.35, 11.00, 13.35, and 13.75 μm; UV (methanol) λ_{max} 272 nm, log ϵ 3.12.

High-resolution MS. Calcd for $C_{12}H_{15}NO_3S$: *m/e* 253.0771. Found: 253.0777.

4-Methoxy-1,6-methanoisoquinoline (2b). Potassium *tert*-butoxide (215 mg, 1.92 mmol) was added to a stirred solution of sulfone imino ether **7** (162 mg, 0.64 mmol) in 10 mL of *tert*-butyl alcohol and heated to 80 °C under nitrogen for 2 h. After cooling to room temperature, water was added and the solution was extracted three times with dichloromethane. The combined organic extracts were washed twice with water and once with saturated sodium chloride, dried over magnesium sulfate, and concentrated to yield 85 mg of a dark oil. Preparative thin-layer chromatography on 2-mm silica gel plates developed with 10% ethyl acetate/hexanes yielded 23 mg (21%) of **2b** as a yellow oil: ^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.05 (d, 1, J = 9.5 Hz, bridgehead H over heterocyclic ring), 0.45 (dd, 1, J = 9.5 Hz, J' = 1.8 Hz, bridgehead H over carbocyclic ring), 3.94 (s, 3, OCH_3), 5.94 (d, 1, J = 1.8 Hz, H α to OCH_3, shown by decoupling to be due to NH), 6.53 (dd, 1, J = 10.1 Hz, J' = 8.4 Hz, carbocyclic-ring H), 6.71 (dd, 1, J = 10.1 Hz, J' = 8.4 Hz, carbocyclic-ring H), 7.26 (d, 1, J = 10.1 Hz, carbocyclic-ring H), 7.37 (d, 1, J = 10.1 Hz, carbocyclic-ring H), 7.44 (s, 1, H α to nitrogen); IR (thin film) 3.50, 3.60, 6.50, 6.98, 7.18, 7.38, 7.66, 7.74, 8.02, 8.32, 8.50, 8.68, 9.18, 9.75, 11.25, 11.50, 12.35, 13.65, 14.35, and 14.85 μm; UV (methanol) λ_{max} 258 (log ϵ 4.33), 320 (log ϵ 3.63) and 385 mμ (log ϵ 3.29).

High-resolution MS. Calcd for $C_{11}H_{11}NO$: *m/e* 173.0840. Found: 173.0838.

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Registry No.—**2b**, 66910-93-8; **3**, 7068-08-8; **4**, 67338-10-7; **5a**, 67272-08-6; **5b**, 67335-64-2; **5c**, 67272-09-7; **6**, 67272-10-0; **7** isomer 1, 67272-11-1; **7** isomer 2, 67335-65-3; **8**, 183-24-4; **9**, 67272-12-2; **10**, 13288-27-2; **11**, 7068-07-7; 12 phenylurethane, 67272-13-3.

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α-Acyl-o-tolunitriles as Intermediates in the Preparation of 3-Substituted Isoquinolines and 1-Amino-2-benzopyrylium Derivatives[1]

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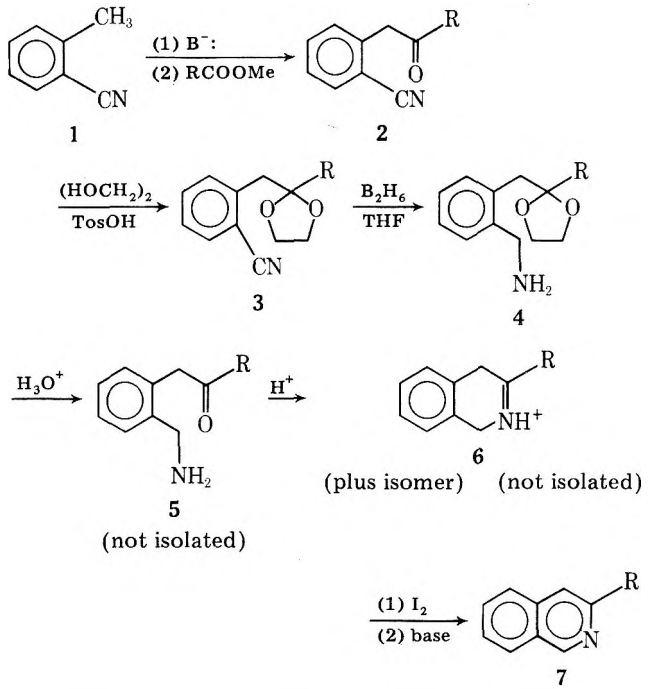
The carbonyl function of α-acyl-o-tolunitriles (2) was protected by reaction with ethylene glycol, and the nitrile function of the resulting 1,3-dioxolanyl derivatives (3) was reduced to the corresponding benzylamine (4). Acid-catalyzed hydrolysis of the protective group of 4 was accompanied by cyclization to afford the easily dehydrogenated 3-substituted dihydroisoquinolines (e.g., 6). Treatment of α-acyl-o-tolunitriles (2) with hydrobromic acid resulted in the first isolation of pure 1-amino-3-aryl-2-benzopyrylium bromides (10). These salts (10) underwent facile hydrolysis to isocoumarins (11) and borohydride reduction (in poor yield) to 3-arylisoquinolines (7).

The study of the polar cycloaddition[2,3] of electron-rich olefins with isoquinolinium salts[4] has indicated the importance of having a substituent at position 3 of the isoquinolinium ion, for without such a substituent complicating side reactions may occur. It was also necessary that there be no substituent at position 1. For this particular substitution pattern, the modified Pomeranz-Fritsch[5] appeared more favorable than the other classical isoquinoline syntheses;[6,7] yet at best it afforded only poor overall yield.

A possible alternate approach to such 3-substituted isoquinolines would be the cyclization of benzylamines having an ortho side chain having a carbonyl group at the β position. Although Campbell[8] had suggested that ortho-substituted benzylamines were probably not suitable starting materials for isoquinoline synthesis, it seemed desirable to test this route.

The discovery independently by Boyce and Levine[9] and by Rash, Boatman, and Hauser[10,11] that o-tolunitrile (1) can be acylated in the presence of a strong base afforded an easy route



to o-cyanobenzyl ketones (2), which differ from the desired benzylamine (5) in lacking four hydrogen atoms. The yields in the acylation step averaged about 50% (based upon the ester) using sodium hydride[10,11] or amide[9,12] as the base, the limiting factor appearing to be the known[13] tendency of the anion to undergo condensation with o-tolunitrile.[9-11] The results are recorded in Table I.

Protection of the carbonyl group during the reduction step was achieved by formation of the 1,3-dioxolane derivatives (3). While the yields were generally high for dioxolane, formation was slower than usual,[14] and in the case of the *tert*-butyl derivative (3; R = *t*-Bu) 11 days of refluxing with ethylene glycol were required to produce a 59% yield (Table II). For the reduction of the nitrile function, lithium aluminum hydride appeared promising since it had been reported[15] to reduce o-tolunitrile to o-methylbenzylamine in 88% yield. Some reduction could be effected by refluxing α-(2-phenyl-1,3-dioxolan-2-yl)-o-tolunitrile (**3a**) with an excess of lithium aluminum hydride, but the yield of amine (**4a**), isolated as the hydrochloride, was only 33%. Better results were obtained with diborane,[16,17] which afforded **4a** hydrochloride in 70.5% yield.

With the exception of **4a** and **4e** (which has the p-dimethylaminophenyl substituent), none of the benzylamines (4) could be isolated as hydrochlorides, and they were submitted directly to the hydrolysis–cyclization procedure.

It had been anticipated that the acid-catalyzed hydrolysis of the dioxolane ring of the benzylamine (**4a**) would be accompanied by ring closure, affording either 3-phenyl-1,4-dihydroisoquinoline (**6a**) or a mixture containing the 1,2-dihydro analogue. The hydrochloride of **4a** was refluxed for 3 h in methanol containing a small quantity of hydrochloric acid. Addition of base afforded a yellow precipitate which was extracted into $CDCl_3$. The ^1H NMR spectrum of the solution indicated the presence of 3-phenylisoquinoline (**7a**) as well as one or more dihydro derivatives. Air was bubbled through the $CDCl_3$ solution for 10 min and the spectrum reexamined, revealing that signals characteristic of the dihydroisoquinolines had disappeared and only signals remained for aromatic protons with a characteristic singlet at δ 9.93.

Since samples of 3-phenylisoquinoline prepared by the air oxidation method proved difficult to purify and since it is known[18] that iodine will dehydrogenate 1,2-dihydroisoquinolines while air oxidizes them to isocarbostyryls,[19] it seemed likely that iodine would be the most desirable reagent for the dehydrogenation step. When the hydrolysis–cyclization was followed by reaction with iodine, the hydrochloride of the benzylamine (**4a**) afforded 3-phenylisoquinoline in 70% yield. For the preparation of the other 3-substituted isoquinolines, reduction of the nitrile group (3 → 4), hydrolysis–cyclization, and dehydrogenation (4 → 7) were carried out without purification of the intermediates; the 3-substituted isoquinoline was isolated as a picrate, from which the base is easily recovered. The results, summarized in Table III, show that the overall yields (4 → 7) are very similar.

The new synthesis of 3-substituted isoquinolines is clearly superior to known syntheses in overall yield, scope, simplicity, and availability of starting materials.

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Table I. Acylation Products

2, R	registry no.	time, h	yield,[b] %	mp, °C	significant ^{1}H NMR data[a] 2′,6′ H[c,d]	CH_2[e]	misc.
(a) C_6H_5	10517-64-3	7	54[f]	110.5–111.5[g]	7.98–8.15 (m)	4.51	
(b) p-$MeOC_6H_4$	13670-86-5	72	41[f]	96–97[h]	7.97 (J = 9 Hz)	4.45	3.83 (s, Me)
(c) p-ClC_6H_4	67237-70-1	8	63[f]	94–94.5	7.97 (J = 8.5 Hz)	4.48	
(d) p-MeC_6H_4	67237-71-2	1	45[i]	101–101.5	8.00 (J = 8 Hz)	4.51	2.39 (s, Me)
(e) p-$Me_2NC_6H_4$	67237-72-3	1	48[i]	170.5–171.5	7.90 (J = 9 Hz)	4.41	3.02 (s, Me)
(f) 3,4-$(MeO)_2C_6H_3$	67237-73-4	1	64[i]	143–143.5	[j]	4.48	3.91 (s, Me), 3.92 (s, Me)
(g) 3,4-$(OCH_2O)C_6H_3$	67237-74-5	1	54[i]	132–133	[j]	4.41	5.97 (s, CH_2)
(h) Me_3C	67237-75-6	2	37[i]	43.5–44		4.05	1.15 (s, Me)
(i) C_2H_5O	67237-76-7	1.8	25[i]	53–53.5		3.83	1.20 (t, Me), 4.16 (q, CH_2)

[a] ^{1}H NMR measurements (δ, $CDCl_3$) using tetramethylsilane as a standard. [b] Yields are based upon the nitrile in the sodium hydride procedure and upon the ester in the amide procedure. The editor has been supplied with acceptable C,H,N analyses for all new compounds (2c–i). [c] With the exception of 2a, in which the 2′,6′ H's appear as a multiplet, all compounds gave signals which (where identifiable) appeared as broad doublets. [d] Other aromatic signals have been omitted. [e] All benzylic methylene signals appeared as singlets. [f] By the sodium hydride procedure. [g] Literature[10] mp 110.5–113 °C. [h] Literature[9] mp 96.0–96.9 °C. [i] Sodium amide procedure. [j] Signals not identified.

Table II. Formation of Dioxolane Derivatives 3

3, R	registry no.	time, h	mp,[a] °C	yield, %	^{1}H NMR[b] CH_2[c]	CH_2CH_2[d]	misc.
(a) C_6H_5	37993-73-0	29	103	95	3.40	3.65	
(b) p-$MeOC_6H_4$	37993-74-1	144	127.5–128.5	86	3.40	3.77	3.75 (s, Me)
(c) p-ClC_6H_4	67237-77-8	72	103.5–104.5	99	3.35	3.75	
(d) p-MEC_6H_4	67237-78-9	48	93–94	96	3.42	3.77	2.34 (s, Me)
(e) p-$Me_2NC_6H_4$	67237-79-0	192	143.5–144	88[e]	3.38	3.74	2.93 (s, Me)
(f) 3,4-$(MeO)_2C_6H_3$	67237-80-3	96	112–113	92	3.38	3.82	3.77 (s, Me)
(g) 3,4-$(OCH_2O)C_6H_3$	67237-81-4	72	103.5–104	95	3.37	3.75	5.92 (s, CH_2)
(h) Me_3C	67237-82-5	264	79.5–80.5	59	3.22	3.00 (t), 3.70 (t)	1.07 (s, Me)

[a] Melting point of analytical sample. The editor has been provided with satisfactory elemental analyses (C,H,N) for all compounds listed. [b] Chemical shifts are in δ ($CDCl_3$) from tetramethylsilane. All aromatic resonances have been omitted. [c] Benzylic methylene groups, all of which appeared as singlets. [d] Except as noted, all signals appeared as singlets. [e] Corrected for recovered ketone.

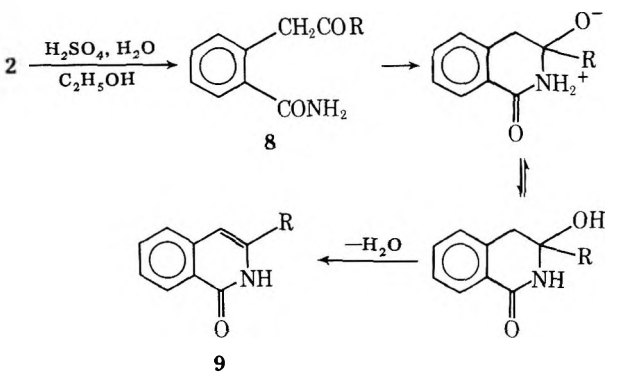
Table III. Conversion of Dioxolanes 3 to 3-Substituted Isoquinoline Picrates and Bases (7)

R	picrate mp, °C	picrate yield, %	picrate registry no.	base mp, °C	base yield, %	base registry no.
(a) C_6H_5	197–199	a	67237-83-6	102.5–103.5[b]	49[c]	37993-76-3
(b) p-$MeOC_6H_4$	243[d]	41	67237-84-7	100.5–101.5[e]	86[f]	20435-81-8
(c) p-ClC_6H_4	243–244[d]	38[g]	67237-86-9	148–148.5	98[f]	67237-85-8
(d) p-MeC_6H_4	256–257[d]	41	67237-88-1	76–76.5	h	67237-87-0
(f) 3,4-$(MeO)_2C_6H_3$	238–240[d]	43	67237-90-5	90.5–92.5	87[f]	67237-89-2
(g) 3,4-$(OCH_2O)C_6H_3$	244–245[d]	45	67237-92-7	131–131.5	96[f]	67237-91-6
(h) Me_3C	156.5–157.5	44[i]	67237-94-9	[j]	93[f]	63144-53-6

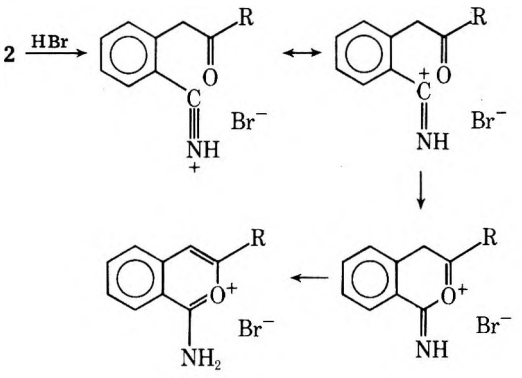
[a] This picrate was obtained from the previously isolated base. It is reported for the purpose of comparison. [b] Literature[20] mp 103–105 °C. [c] This is the overall yield of the base from 3a. [d] With decomposition. [e] Literature[21] mp 95 °C. [f] Yield from picrate. [g] The borane reduction step was carried out as usual except that 14 days were required at room temperature. [h] Not recorded. [i] The hydrolysis and cyclization step involved a 12-h reflux in methanol–hydrochloric acid. [j] The base, which did not crystallize, was converted to the methiodide, mp 222 °C.

While our method provides the best route from α-acyl-o-tolunitriles (2) to the isoquinolines, it was demonstrated earlier[9] that the related isocarbostyryls may be prepared from the same starting materials in 82–90% yield by the action of sulfuric acid in 95% ethanol. The mechanism proposed by the earlier authors suggested that the route of the reaction from the nitrile (2) to the isocarbostyryl (9) passed through the amide 8.

Experiments carried out here on the α-acyl-o-tolunitriles (2) using modified Ritter[22] conditions (48% hydrobromic acid at room temperature) gave instead of the isocarbostyryls (9) the salts which had the composition expected from the addition of 1 mol of hydrogen bromide to 1 mol of the nitrile (2).



From the spectra and reactions of the salts, it seems that these must be 1-amino-3-substituted benzo[c]pyrylium salts (**10**). For the phenyl derivative (**10**; R = Ph), the UV absorption spectrum indicated a highly conjugated system, the IR spectrum showed no identifiable carbonyl or nitrile absorptions, and the ^{1}H NMR spectrum showed signals in the δ 7.53–8.78 region only.



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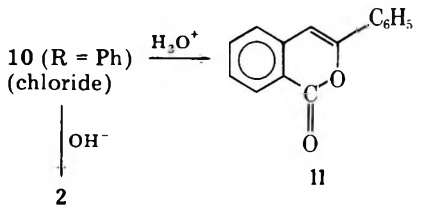
Compound **10** (R = Ph) has never before been isolated in a pure condition, although its existence as a chloride salt had been postulated by Berti[23] as a probable component in an unseparable mixture. Berti's conjecture that it was the 1-amino-3-phenylbenzo[c]pyrylium salt (**10**; R = Ph) in the mixture which afforded 3-phenylisocoumarin (**11**) on acid



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hydrolysis and 2-phenacylbenzonitrile (**2**) on alkaline hydrolysis is fully borne out by our observations on the behavior of pure **10** (R = Ph). It was found that even in the absence of acid the addition of water to a warm solution of the pure pyrylium salt (**10**; R = Ph) in dimethyl sulfoxide afforded the isocoumarin **11** in 88% yield. The action of aqueous ammonia on the pure pyrylium salt **10** at room temperature for 24 h gave 2-phenacylbenzonitrile (**2**) in 79% yield. Apparently, proton abstraction followed by reversion to the keto nitrile structure is favored over the formation of 1-amino-3-phenylisoquinoline.

A brief investigation of the action of sodium borohydride in methanol at 0 °C on the 1-amino-3-arylbenzo[c]pyrylium salts showed that a complex mixture containing a small quantity of 3-arylisoquinoline (17%, R = Ph; 29%, R = *p*-$CH_3OC_6H_4$) was formed, but the major products appeared to be the *o*-phenacylbenzonitriles (**2**) or the corresponding secondary alcohols. The reaction appeared to offer little promise as a practical route to isoquinoline derivatives.

Experimental Section

The elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. UV absorption spectra were taken with a Beckman Model DB-G spectrophotometer. IR spectra of solids (KBr discs) and liquids (neat) were taken with a Perkin Model 237 spectrometer. ^{1}H NMR spectra were obtained at 60 MHz with Varian T-60 or A-60 spectrometers using tetramethylsilane as an internal standard.

General Procedures for the Preparation of α-Acyl-o-tolunitriles (2). A. By the Sodium Hydride Procedure. This method is an adaptation of that described by Rash.[11] A stirred slurry of 4 equiv of sodium hydride (57% dispersion in mineral oil) in 1,2-dimethoxyethane (monoglyme) was refluxed under nitrogen. A solution of 1 equiv of *o*-tolunitrile and 1 equiv of ester in monoglyme was added to the slurry. The mixture was refluxed under nitrogen for 7–72 h (Table I), after which time most of the solvent was removed under reduced pressure. Ether and water were added to the residue. A portion of the product is often ether-insoluble, and this material was isolated by filtration. The ethereal solution in any case was separated and dried. The ether was evaporated and the residue recrystallized from ethanol (Table I).

B. By the Sodium Amide Procedure. This method is an adaptation of that of Boyce and Levine.[9] Sodium amide was prepared by adding 2 equiv of sodium metal to a large excess of anhydrous liquid ammonia with a crystal of ferric nitrate added as catalyst. A solution of 2 equiv of *o*-tolunitrile in anhydrous ether was added. After sufficient time for anion formation (about 15 min), a solution of 1 equiv of ester was added. The mixture was stirred for 1–2 h (Table I). The reaction was quenched with 2 equiv of ammonium chloride. After evaporation of the ammonia, ether and water were added. Products insoluble in the ether–water mixture were isolated by filtration. Others were obtained from the ether extract, usually by recrystallization.

Preparation of Dioxolane Derivatives (3) of Keto Nitriles (2). In a reflux apparatus provided with a Dean-Stark trap, 0.2 mol of the keto nitrile **2** was dissolved in a mixture of 300 mL of anhydrous benzene and 49.6 g (0.8 mol) of ethylene glycol. *p*-Toluenesulfonic acid (0.4 g) was added, and the mixture was refluxed until approximately the theoretical quantity of water had been collected (Table II). The benzene solution was washed with bicarbonate solution and water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was pure enough for use in the next step, but it could be recrystallized from ethanol.

Borane Reduction of α-(2-Substituted-1,3-dioxolan-2-yl)-o-tolunitrile (3 → 4). In a three-neck flask equipped with a condenser, drying tube, nitrogen inlet, and an addition funnel was placed 0.02 mol of the dioxolane derivative. After the system had been flushed with nitrogen, 20 mL of 1 M borane in tetrahydrofuran was added and the solution was allowed to stand at room temperature for 24 hr. Then an additional 10 mL of borane–tetrahydrofuran was added, and after 24 h it was quenched by the addition of 30 mL of ethanol. Most of the solvents were removed under reduced pressure, except in the case of **3** (R = Ph) where the crude amine was subjected directly to hydrolysis and cyclization.

***o*-[(2-Phenyl-1,3-dioxolan-2-yl)methyl]benzylamine (4a) Hydrochloride.** The crude amine **4a** obtained from nitrile **3a** was dissolved in ethanol and precipitated as the salt by passing hydrogen chloride through the solution for 10 min. The colorless precipitate was collected and dried to give 4.3 g (70.5%) of the hydrochloride salt (**4a**·HCl) in an analytically pure condition: mp 189–190.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.25 (s, 2, CH_2), 3.65 (s, 4, CH_2CH_2), 4.05 (s, 2, CH_2N), 7.14–7.60 (m, 9, aromatic), 8.80 (brd s, 3, NH_3^+).

Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.70; H, 6.60; N, 4.40.

Hydrolysis and Cyclization of Benzylamine 4a Hydrochloride. A solution of 2.0 g (0.0066 mol) of the hydrochloride salt of benzylamine **4a** was refluxed for 10 min in a mixture containing 20 mL of methanol, 40 mL of water, and 1 mL of hydrochloric acid. The mixture was concentrated under reduced pressure to half volume and then basified with sodium hydroxide solution. The yellow precipitate was taken up in chloroform, and the solution was washed twice with water before adding 35 mL of a 0.2 M solution of iodine in chloroform. The mixture was allowed to stand for 45 min, and then excess iodine was removed by washing the solution with sodium bisulfite solution. Evaporation of the solvent yielded 1.3 g of crude product which on recrystallization from ethanol–water afforded 0.95 g (70%) of 3-phenylisoquinoline, mp 99–102 °C. An analytical sample was recrystallized from ethanol: mp 102.5–103.5 °C (lit.[20] mp 103–105 °C); UV max (95% ethanol) 328, 290, 250 nm.

When the hydrolysis–cyclization was carried out essentially as described above but without the treatment with iodine in chloroform and the ^{1}H NMR spectrum ($CDCl_3$) of the product was taken immediately, the spectrum was complex: δ 3.10 (brd s, 2), 3.85 (brd t, 2), 4.55 (s, 2), 4.95 (brd t, 2), 5.85 (s, 1), 7.03–8.23 (m), 9.33 (s, 1). Air was bubbled through the ^{1}H NMR sample for 10 min, and a second spectrum was recorded, δ 7.02–8.17 (m, 14) and 9.27 (s, 1), indicating that the product was almost entirely aromatic.

General Procedure for Hydrolysis, Cyclization, and Aromatization of Ortho-Substituted Benzylamines (4 → 7). The crude amine **4** from the reduction procedure was dissolved in 40 mL of methanol and 4 mL of water, 1 mL of concentrated hydrochloric acid was added, and the mixture was refluxed for 3 h. The solution was concentrated and made basic and the product taken up in ether or

chloroform. The solution was washed with water, 35 mL of a solution of iodine in chloroform was added, and the mixture was allowed to stand for approximately 45 min. Excess iodine was removed by washing the solution with a 5% sodium bisulfite solution. The solvent was removed and the residue taken up in a minimum quantity of ethanol. Addition of an ethanolic solution of picric acid caused the precipitation of the picrate. Analytical samples of the picrates were prepared by crystallization from acetonitrile. The results are summarized in Table III.

1-Amino-3-phenyl-2-benzopyrylium Bromide (10; R = Ph). A. By 48% Hydrobromic Acid. A heterogeneous mixture of 3.0 g (0.014 mol) of powdered α-benzoyl-o-tolunitrile (**2a**) and 90 mL of 48% hydrobromic acid was stirred at room temperature for 72 h. Water (30 mL) was added and the yellow precipitate removed by filtration. The product was dried at 72 °C (0.7 mm) to afford 3.7 g (88%) of **10** (R = Ph), mp 292–294 °C dec. An analytical sample crystallized from anhydrous methanol as yellow needles: mp 292–294 °C dec; UV max (95% ethanol) 360 (sh), 348, 312, 300, 264 (sh), 256, 238 (sh), 220 nm; IR (Nujol) C≡N and C=O absent.

B. By Hydrogen Bromide. A slightly less pure product (mp 288–292 °C) was obtained in 83% yield when dry hydrogen bromide was passed for 20 min through a solution of **2a** in acetic anhydride.

Anal. Calcd for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64. Found: C, 59.79; H, 3.97; N, 4.48.

3-Phenylisocoumarin (11). To a solution of 2.0 g of the benzopyrylium derivative **10** (R = Ph) in a minimum quantity of warm dimethyl sulfoxide was added water until cloudiness persisted. On cooling, off-white crystals formed which were collected and dried to afford 1.3 g (88%) of 3-phenylisocoumarin (**11**), mp 81.5–82 °C. Recrystallization from methanol–water gave colorless needles, mp 86–86.5 °C (lit.[24] mp 90–91 °C). A mixture melting point with an authentic sample[25] was undepressed: ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 1, H-8), 7.27–7.93 (m, 8, aromatic), 6.90 (s, 1, H-4).

When α-benzoyl-o-toluic acid[25] was subjected to the same conditions, only the starting material was recovered.

Basic Hydrolysis of the Benzopyrylium Derivative 10 (R = Ph). To 0.5 g of the bromide salt **10** (R = Ph) was added 50 mL of 22% aqueous ammonia, and the mixture was stirred at room temperature for 24 h. An off-white solid, 0.28 g (79%), was collected, and upon recrystallization from ethanol–water it was shown by mixture melting point to be α-benzoyl-o-tolunitrile (**2**; R = Ph). The use of triethylamine instead of ammonia afforded the same product (**2**; R = Ph) in 85% yield.

1-Amino-3-(*p*-methoxyphenyl)-2-benzopyrylium Bromide (10; R = *p*-MeOC$_6$H$_4$). This was prepared as in the case of the prototype **10** (R = Ph) (85% yield) by the use of hydrobromic acid: mp 278–279 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.87 (s, 3, Me), 7.11 (brd d, 2, J = 8.5 Hz, H-3′ and H-5′), 7.68–8.15 (m, 8, NH_2 and aryl H), 8.51 (m, 1, OH).

Anal. Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 58.07; H, 4.01; N, 3.97.

Hydrolysis of the salt (**10**; R = p-MEOC$_6$H$_4$) was carried out as in the case of the prototype (R = Ph), affording 3-(*p*-methoxyphenyl)-isocoumarin in 84% yield: mp (pure) 119–121 °C (lit.[26] mp 116–122 °C); ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3, OCH_3), 6.78 (s, 1, H-4), 6.93 (brd d, 2, H-3′ and H-5′), 7.27–7.87 (m, 5, aromatic), 8.18–8.35 (m, 1, H-8).

1-Amino-3-(3′,4′-dimethoxyphenyl)-2-benzopyrylium Bromide (10; R = 3′,4′-(MeO)$_2$C$_6$H$_3$). This was prepared (94% yield) as in the case of the analogues **10**: mp 269.5 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.85 (s, 3, Me), 3.89 (s, 3, Me), 7.12 (d, 1, J = 8 Hz, H-5′), 7.57–8.05 (m, 8, NH_2 and aromatic), 8.45–8.62 (m, 1, H-8).

Anal. Calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.19; H, 4.55; N, 3.68.

Hydrolysis of the salt (**10**; R = 3′,4′-(MeO)$_2$C$_6$H$_3$) was carried out as in the case of the analogues, affording 3-(3′4′-dimethoxyphenyl)-isocoumarin in 95% yield: mp 116 °C (lit.[27] mp 119 °C); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3, OCH_3), 3.95 (s, 3, OCH_3), 6.80 (s, 1, H-4), 6.9 (d, 1, H-5′), 7.17–7.73 (m, 5, aromatic), 8.20–8.37 (m, 1, H-8).

Reduction of 1-Amino-3-phenyl-2-benzopyrylium Bromide (10; R = Ph). Addition of a solution of 0.062 g (1.7 mmol) of sodium borohydride in 20 mL of anhydrous methanol to an ice–cold solution of 1 g of **10** (R = Ph) in 75 mL of methanol was carried out dropwise. The resulting mixture was kept in an ice bath for 2 h at room temperature for 1 h. Most of the methanol was removed under vacuum, a little water was added, and the organic fraction was taken up in ether. The ethereal solution was evaporated, the residue taken up in ethanol, and an ethanol solution of picric acid added. The picrate of 3-phenylisoquinoline (0.25 g, 17%) crystallized, mp 196–197 °C (melting point was undepressed when mixed with an authentic sample).

Reduction of 1-Amino-3-(*p*-methoxyphenyl)-2-benzopyrylium Bromide (10; R = *p*-MeOC$_6$H$_4$). When the *p*-methoxyphenyl salt (**10**; R = p-MeOC$_6$H$_4$) was reduced, 3-(*p*-methoxyphenyl)isoquinoline (**7b**) was isolated as the picrate (29% yield), mp 233–235 °C. Recrystallized from acetonitrile, it gave no depression in a mixture melting point with an authentic sample, mp 240–242 °C.

Registry No.—**1**, 529-19-1; **4a**, 37993-75-2; **4a**-HCl, 67237-95-0; **4b**, 67237-96-1; **4c**, 67237-97-2; **4d**, 67237-98-3; **4e**, 67237-99-4; **4f**, 67238-00-0; **4g**, 67238-01-1; **4h**, 67238-02-2; **10** (R = Ph), 67238-03-3; **10** (R = p-MeOC$_6$H$_4$), 67238-04-4; **10** (R = 3′,4′-(MeO)$_2$C$_6$H$_3$), 67238-05-5; **11**, 4809-08-9; RCOOME (R = C_6H_5), 93-58-3; RCOOMe (R = p-MeOC$_6$H$_4$), 121-98-2; RCOOMe (R = p-ClC$_6$H$_4$), 1126-46-1; RCOOMe (R = p-MeC$_6$H$_4$), 99-75-2; RCOOMe (R = p-Me$_2$NC$_6$H$_4$), 1202-25-1; RCOOMe (R = 3,4-(MeO)$_2$C$_6$H$_3$), 2150-38-1; RCOOMe (R = 3,4-(OCH$_2$O)C$_6$H$_3$), 326-56-7; RCOOMe (R = Me_3C), 598-98-1; RCOOMe (R = C_2H_5O), 623-53-0; ethylene glycol, 107-21-1; 3-(*p*-methoxyphenyl)isocoumarin, 29910-92-7; 3-(3′,4′-dimethoxyphenyl)isocoumarin, 22073-92-3.

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Synthesis of Some 2-Aminofurans from Cyanoacetone Enolate and Their Rearrangement to 3-Cyanopyrroles with Ammonia

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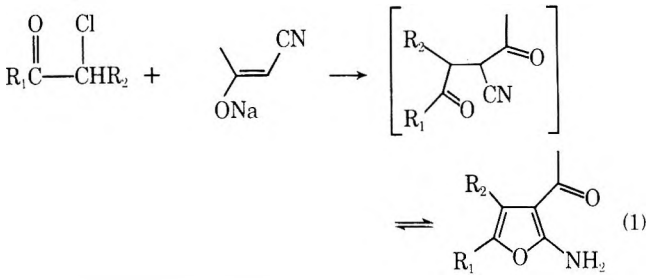
Condensation of the sodium enolate of cyanoacetone with α-chloro ketones having a nitrile, ester, ketone, or amide group on the carbon atom bearing the chlorine gave 2-aminofurans, 2-hydroxypyrroles, or 2-hydroxyfurans depending on the group present in the chloro ketone. Reaction of 2-amino-3-acetylfurans with ammonia produced rearranged pyrroles having methyl and cyano groups in the 2 and 3 positions, respectively. The structures assigned were proven by X-ray crystallography of a representative product, 2-amino-3-acetyl-4-cyano-5-methylfuran.

Cyanoacetone[1] is a compound lacking in both stability and availability and accordingly has rather limited utility in preparative organic chemistry. In contrast, the sodium enolate is readily available as a dry powder from 5-methylisoxazole[2] and can be stored indefinitely. While investigating the chemistry of this stable derivative, an easily accessible group of 2-aminofurans was discovered.[3]

The condensation reaction involved is shown in eq 1 in



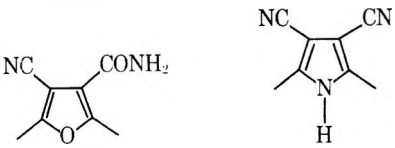
(1)

generalized form. Related condensations utilizing malononitrile and ethyl cyanoacetate were reported by Westöö in 1959.[4] In the examples studied, R_1 is a methyl group. In the successful cases, R_2 is a nitrile, ester, or ketone function and evidently needs to be an electron-withdrawing group of this sort.

The aminofuran **4** was obtained in the first instance as a byproduct in the preparation of α-chloro-α-cyanoacetone (**3**). The formation of **4** was the result of incomplete chlorination of 5-methylisoxazole as shown in Scheme I.[5]

The aminofuran **4** can be prepared quite simply by chlorinating half of any given quantity of 5-methylisoxazole followed by treatment of the resulting mixture with NaOEt in EtOH and heating the resulting precipitate of sodium enolates in water buffered with $NaHCO_3$.

The structure of compound **4** could not be unequivocally assigned on the basis of spectral and analytical data. For example, the (incorrect) carboxamide structure **5**, suggested obliquely by the reaction (of **4**) with hot aqueous ammonia to give the known[6] pyrrole **6**, was a possible alternative. To clear

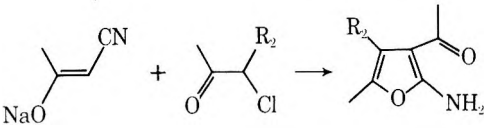


5 **6**

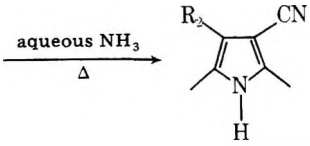
up the structural ambiguity regarding the position of substituents on the furan ring, an X-ray crystallographic structure determination was carried out, proving that the aminofuran structure **4** was correct (Figure 1).

The reorganization of functional groups occurring during the transformation of the furan **4** into the pyrrole **6** is assumed to proceed through the open dicyano–diketone. A published analogy to this rearrangement is the base-induced rearrangement of ethyl 2-amino-4-phenylthiophene-3-carboxylate to 2-hydroxy-3-cyano-4-phenylthiophene.[7]

The corresponding aminofurans **9** and **11** were obtained when the cyanoacetone enolate was condensed with ethyl 2-chloroacetoacetate and with 3-chloro-2,4-pentanedione. These products also rearranged to cyanopyrroles by treatment with ammonia.

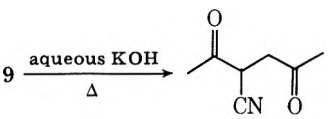


7, R_2 = COOEt **9**, R_2 = COOEt
8, R_2 = $COCH_3$ **11**, R_2 = $COCH_3$



10, R_2 = COOEt
12, R_2 = $COCH_3$

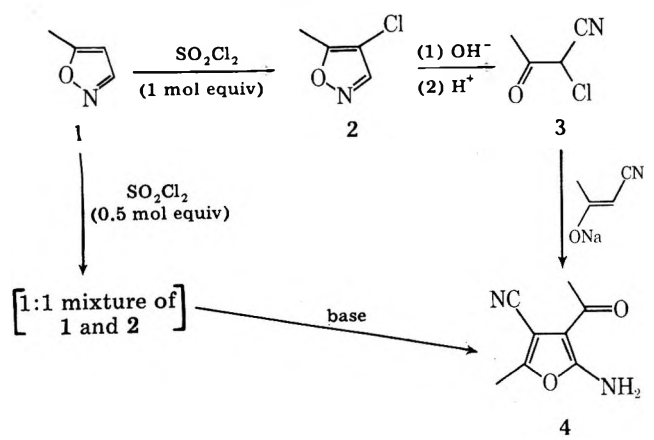
A result which supports the contention that reversal of the furan ring closure is involved in the rearrangement was obtained by heating the ester **9** with aqueous potassium hydroxide, which yielded 3-cyano-2,5-hexanedione (**13**).



13

When the group R_2 in the generalized reaction was a primary amide group, an alternative mode of cyclization prevailed and a hydroxypyrrole was obtained rather than an aminofuran. The product in this case, compound **15**, aggres-

Scheme I



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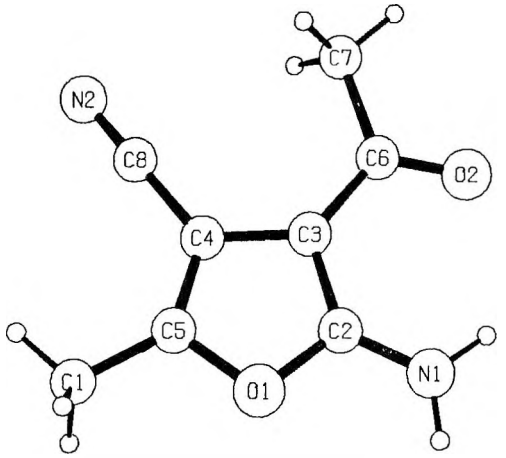
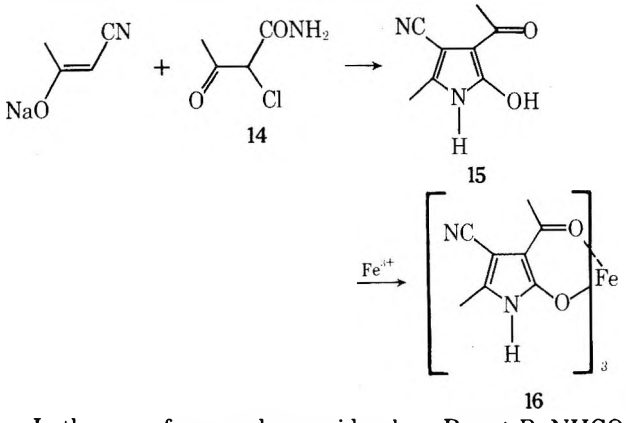
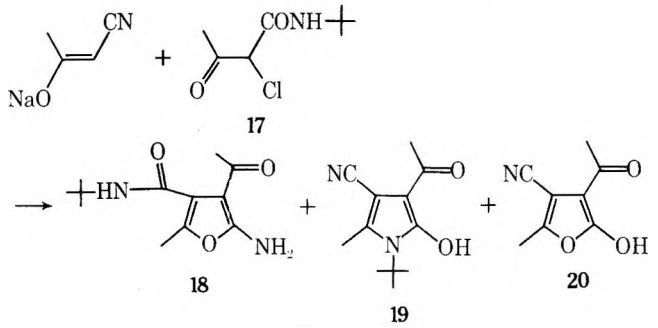


Figure 1. X-ray crystallographic structure of **4**.

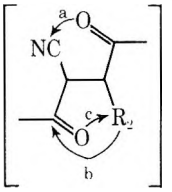
sively chelates iron, forming the dark purple tris complex **16**. The affinity of **15** for even trace amounts of iron leaves vacuum sublimation as the most practical method of preparing colorless samples. Compound **15** was unchanged by exposure to hot aqueous ammonia.



In the case of a secondary amide where R_2 = *t*-BuNHCO–, the existence of three competing modes of cyclization became evident, resulting in a mixture of the products **18**, **19**, and **20**.



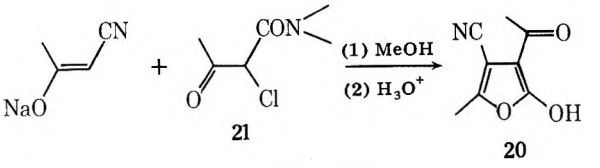
Compounds **18** and **19** are the result of cyclization modes



R_2	cyclization mode
CN	a
COOEt	a
$COCH_3$	a
$CONH_2$	b
CONHBu-*t*	a, b, c
$CONMe_2$	c

a and b encountered in the earlier examples. Compound **20** results from cyclization mode c followed by elimination of *tert*-butylamine from the tetrahedral intermediate.

Finally, when the group R_2 is a tertiary amide group, i.e., dimethylamide, the chemistry reverts to the simple situation in which a single product is formed. Cyclization mode c prevails, and the hydroxyfuran **20** is obtained in good yield.



Experimental Section[9]

α-Chloro-α-cyanoacetone (3). 5-Methylisoxazole (83 g, 1 mol) was treated with sulfuryl chloride (155 g, 1.15 mol) dropwise through a condenser at such a rate as to maintain a gentle reflux. Upon completion of the addition, refluxing was continued for 1 h by heating. After cooling, the flask was connected to a water aspirator for a brief period to remove HCl and SO_2. The crude 4-chloro-5-methylisoxazole (114 g) was added to a solution of NaOH (60 g, 1.5 mol) in water (500 mL) and rinsed in with more water (200 mL). This mixture was swirled with intermittent cooling in such a way as to let the reaction proceed without getting hot. When a clear solution had formed, it was chilled in ice and treated with 200 mL of concentrated hydrochloric acid (ca. 2 mol). The resulting yellow solution was saturated with NaCl and extracted three times with ether. The combined extracts were dried over Na_2SO_4, and the ether was evaporated. Distillation of the residue at 20 mm gave 89 g (76%) of colorless liquid distilling mostly at 85 °C; the temperature rose quickly to 100 °C near the end of the distillation. The product partly crystallized to a slush on standing in the refrigerator. A sample of the crystals washed with ether/hexane had mp 32–37 °C: IR (neat liquid) 3200, 2230, 1745, and 1630 cm^{-1} (the spectrum of the solid (Nujol) is very similar but with a much more intense band at 1625 cm^{-1} than at 1745 cm^{-1}); NMR ($CDCl_3$) four singlets at 2.20 (CH_3, enol), 2.46 CH_3, ketone), 5.01 (CH, ketone), and 7.10 (OH, enol) ppm. The peaks ascribed to the ketone are stronger when the NMR solution is prepared from a liquid specimen, and those ascribed to the enol are stronger when a solid specimen is used. The mass spectrum had peaks at *m/e* 117 (M^+) and 43 (100); the UV spectrum in EtOH had a λ_{max} 234 mμ (ε 10 550).

Anal. Calcd for C_4H_4ClNO: C, 40.87; H, 3.43; Cl, 30.16; N, 11.92. Found: C, 40.76; H, 3.59; Cl, 29.47; N, 11.32.

2-Amino-3-acetyl-4-cyano-5-methylfuran (4). (a) A solution of α-chloro-α-cyanoacetone (13.7 g, 0.117 mol) and the sodium enolate of cyanoacetone (12.5 g, 0.119 mol) in water (150 mL) was heated on the steam bath for 30 min. The orange-yellow precipitate which formed on cooling was filtered, washed with water, air-dried (10.8 g), and taken up in CH_2Cl_2, some insoluble material being discarded. The solution was concentrated with the addition of hexane to give after chilling 9.0 g (47%) of colorless crystals with mp 182–184 °C: IR (Nujol) 3250, 2240, 1675, 1635, 1600, and 1510 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6/D_2O washed) 2.40 and 2.43 ppm (singlets) (before the D_2O wash, the NH_2 signal appeared at 7.4 ppm and the CH_3 singlets were not resolved); mass spectrum, *m/e* 43 (100), 149, and 164 (M^+).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.60; H, 4.95; N, 16.97

(b) Sulfuryl chloride (13.5 g, 0.1 mol) was added gradually through a condenser to 5-methylisoxazole (16.6 g, 0.2 mol). The mixture was heated on a steam bath for 1 h and then chilled in ice. A sodium ethoxide solution prepared by dissolving sodium (5 g) in ethanol (100 mL) was added dropwise with stirring and continued cooling. After dilution with ether, the precipitated salts were collected and dissolved in water (200 mL) containing sodium bicarbonate (10 g). Heating and workup as in (a) afforded 5.75 g (35%) of compound **4** in two crops.

2,5-Dimethyl-3,4-dicyanopyrrole (6). A mixture of aminofuran **4** (6.3 g) and concentrated aqueous ammonia (125 mL) was stirred at reflux for 14 h. The precipitate which formed was collected after cooling and air-dried to give 3.9 g of crude product. Purification by vacuum sublimation afforded 3.3 g (59%) of very pale yellow crystals with mp 247–248 °C (lit.[6] mp 239 °C): IR (Nujol) 3200, 2230, 1615, and 1540 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 2.34 (s, 6 H) and 11.5 (broad, 1 H) ppm; mass spectrum, *m/e* 144 (100) and 145 (M^+).

Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.09; H, 5.04; N, 28.72.

2-Amino-3-acetyl-5-methyl-4-furancarboxylic Acid Ethyl

Ester (9). A solution of the sodium enolate of cyanoacetone (10.5 g, 0.1 mol) and ethyl 2-chloroacetoacetate (16.5 g, 0.1 mol) in water (100 mL) was heated on the steam bath for 90 min. The brownish precipitate which formed on cooling was collected (15.5 g) and taken up in ethanol. Some insoluble material was filtered off, and the filtrate was concentrated by boiling with the addition of water. The product separated in colorless leaflets, giving 9.95 g (47%) with mp 147–149 °C: IR (Nujol) 3400, 3100, 1720, 1650, and 1620 cm^{-1}; NMR ($CDCl_3$) 1.38 (t, 3 H, J = 7 Hz), 2.40 (s, 6 H), 4.36 (q, 2 H), and 6.4 (broad s, 2 H) ppm; mass spectrum, m/e 43 (100), 165, and 211 (M^+).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.97; H, 6.18; N, 6.59.

2,5-Dimethyl-4-cyanopyrrole-3-carboxylic Acid Ethyl Ester (10). A mixture of compound **9** (5.5 g) in concentrated aqueous ammonia (100 mL) was stirred at reflux for 4 h. After cooling, the precipitate was collected and air-dried, giving 4.4 g of crude product. Recrystallization from methylene chloride/ethanol/hexane gave 3.25 g (65%) of colorless crystals with mp 150–152 °C (lit.[6] mp 152 °C); IR (Nujol) 3200, 2220, and 1675 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) 1.40 (t, 3 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 4.33 (q, 2 H), and 11.0 (broad, 1 H) ppm; mass spectrum, m/e 147, 163 (100), and 192 (M^+).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.21; N, 14.62.

2-Amino-3,4-diacetyl-5-methylfuran (11). A solution of 3-chloro-2,4-pentanedione (26 g, 0.2 mol) and the sodium enolate of cyanoacetone (21 g, 0.2 mol) in water (100 mL) and methanol (200 mL) was heated to reflux on a steam bath for 90 min. Concentration under reduced pressure and chilling formed a precipitate which was collected, washed with water, and air-dried. An orange-red impurity was removed by trituration with methylene chloride, leaving 13.1 g (36%) of pale yellow needles with mp 168–169 °C: IR (KBr) 3375, 1660, and 1640 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) 2.17 (s, 3 H), 2.33 (s, 3 H), 2.44 (s, 3 H), and 7.4 (broad s, 2 H) ppm; mass spectrum, m/e 43 (100) and 181 (M^+).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.69; H, 5.99; N, 7.95.

2,5-Dimethyl-3-cyano-4-acetylpyrrole (12). Compound **11** (13.1 g) and concentrated aqueous ammonia (200 mL) were heated to reflux for 90 min. After cooling, the product was collected and dried to give 6.8 g (58%) of pink-white crystals. Recrystallization from methanol gave colorless crystals with mp 214–216°C: IR (KBr) 3210, 3145, 2215, and 1625 cm^{-1}; NMR (Me_2SO-d_6) 2.27 (s, 3 H), 2.37 (s, 6 H), and 11.80 (broad, 1 H) ppm; mass spectrum, m/e 147 (100) and 162 (M^+).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.75; H, 6.11; N, 17.16.

3-Cyano-2,5-hexanedione (13). A solution prepared from compound **9** (40 g), potassium hydroxide (80 g), water (100 mL), and methanol (400 mL) was heated at reflux for 4 h. After cooling, the solution was acidified with 3 N HCl and water and methanol were evaporated under reduced pressure. The residue was extracted with ethanol. The extract was filtered and evaporated, and the resulting residue was extracted with methylene chloride. This extract was filtered and evaporated, and the residue was vacuum distilled to give 16.25 g of impure product. Chromatography on silica gel (1 kg) afforded 12 g of material which on redistillation gave 9.2 g (35%) of pale yellow liquid with bp 71–78 °C (0.1 mm) [lit.[10] bp 106–108 (3 mm) and 137–138 °C (15–16 mm)]: IR (film) 3300 (enol), 2260, 2220 (enol), and 1725 cm^{-1}; NMR ($CDCl_3$) 2.17 (s, 3 H), 2.42 (s, 3 H), 3.03 (m, eight lines, J_{AB} = 18.0 Hz, J_{AX} = 5.3 Hz, and J_{BX} = 6.5 Hz, 2 H), and 3.79 (m, four lines, 1 H) ppm; mass spectrum, m/e 43 (100) and 139 (M^+).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 59.93; H, 6.64; N, 9.85.

2-Chloroacetoacetamide (14). α-Chloro-α-cyanoacetone (80 g) was combined with concentrated HCl (100 mL) and cooled in ice to control the exothermic hydrolysis. After standing overnight, a precipitate of ammonium chloride was filtered out and washed with ether. The filtrate was evaporated to a small volume, and ether was added. This mixture was dried with Na_2SO_4, filtered, and evaporated, and the residue was taken up in warm CH_2Cl_2, dried again, and evaporated. The residue solidified on standing; it was triturated with a small volume of CH_2Cl_2, filtered, washed with CH_2Cl_2, and then dried to give 28.5 g (31%) of the amide (in three crops). An analytical sample prepared by vacuum sublimation had mp 78–85 °C (lit.[11] mp 76–77 °C): IR ($CHCl_3$) 3200–3500, 1730 (shoulder), 1650, 1630, and 1575 cm^{-1}; NMR ($CDCl_3$) 2.11 and 2.40 (CH_3 of ketone and enol), 4.80 (CH of ketone), and 6.5 (broad, NH_2 and OH of enol) ppm; mass spectrum, m/e 43 (100) and 135 (M^+).

Anal. Calcd for $C_4H_6ClNO_2$: C, 35.44; H, 4.46; Cl, 26.15; N, 10.33. Found: C, 35.39; H, 4.50; Cl, 26.31; N, 10.36.

2-Hydroxy-3-acetyl-4-cyano-5-methylpyrrole (15). A solution prepared from 2-chloroacetoacetamide (1.35 g), the sodium enolate of cyanoacetone (1.05 g), and sodium bicarbonate (0.85 g) in *distilled* water (20 mL) was heated on a steam bath for 45 min. The solution was cooled, diluted with distilled water, and acidified with 3 N HCl. The product was collected, washed with water, and air-dried to give 1.2 g (73%) of light tan powder. A sublimed sample gave pale yellow crystals with mp 206–209 °C: IR (Nujol) 3100, 2200, 1655, and 1620 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) 2.17 (s, CH_3), 2.30 (s, CH_3), 8.4 (broad, NH or OH), and 11.2 (broad, NH or OH) ppm; mass spectrum, m/e 164 (100, M^+).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.97; H, 5.18; N, 17.52.

Iron(III) Complex of 2-Hydroxy-3-acetyl-4-cyano-5-methylpyrrole (16). A solution of compound **15** (1 g) in ethanol (20 mL) was treated dropwise with excess ferric acetate in ethanol. The latter was prepared by dissolving ferric chloride (2 g) in ethanol (25 mL) and adding sodium acetate (5 g) followed by removal of sodium chloride by filtration. The purple solution of the complex was diluted to 250 mL with water, and the precipitate was collected on Whatman No. 42 filter paper. After washing and drying, 1.2 g of product was obtained. Recrystallization (a) from chloroform and (b) from acetone/hexane gave 900 mg (81%) of dark purple fine needles with mp >330 °C: IR (KBr) 3270, 2215, 1610, 1580, and 1510 cm^{-1}; UV-vis (CH_2Cl_2) 240 nm (ϵ 24 750), 255 sh (19 600), 296 (15 355), 340 sh (8135), and 555–565 (3820).

Anal. Calcd for $C_{24}H_{21}FeN_6O_6$: C, 52.86, H, 3.88; N, 15.41; Fe, 10.24. Found: C, 52.22; H, 3.99; N, 15.49; Fe, 10.56.

2-Chloro-*N*-*tert*-butylacetoacetamide (17). Diketene (42 g, 0.5 mol) was mixed with ca. 200 mL of ice and water in a 2-L three-neck flask. A solution of *tert*-butylamine (37.5 g, 0.5 mol) in water (150 mL) was added gradually with stirring, and more ice was added as needed to keep the reaction at or below 20 °C. The solution was stirred for 20 min after completing the addition, acidified with concentrated HCl (400 mL), and cooled to 10 °C with an ice/acetone bath. Aqueous sodium hypochlorite ("Chlorox"; 750 mL, 0.5 mol) was then added dropwise with rapid mechanical stirring. The product was filtered out, washed with water, and air-dried for several hours to give 78.5 g (81.8%) of colorless solid. An analytical sample was recrystallized from methylene chloride/hexane to give colorless crystals with mp 105–108 °C: IR (Nujol) 3300, 3100, 1750, 1660, and 1570 cm^{-1}; NMR ($CDCl_3$) 1.44 (s, 9 H), 2.43 (s, 3 H), 4.73 (s, 1 H), and 6.4 (broad, NH) ppm; mass spectrum, m/e 57 (100) and 191 (M^+).

Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; Cl, 18.50; N, 7.31. Found: C, 50.31; H, 7.44; Cl, 18.44; N, 7.17.

Condensation of Cyanoacetone Sodium Enolate with Compound 17. Preparation of 18, 19, and 20. A mixture of **17** (19.2 g, 0.1 mol) and cyanoacetone sodium enolate (10.5 g, 0.1 mol) in water (100 mL) was heated on the steam bath. Addition of sodium bicarbonate (10 g) led to the formation of a clear brown solution. Heating was continued for 1 h, during which time small amounts of solid material subliming on the flask wall were washed back in with a little ethanol (6 mL). Pale yellow platelets of 2-amino-3-acetyl-4-(*N*-*tert*-butylcarboxamide)-5-methylfuran (**18**) separated upon chilling. These were collected, washed with water, and air-dried to give 2.1 g (8.8%) of **18**. A sample recrystallized from aqueous ethanol had mp 63–67 °C: IR ($CHCl_3$) 3480, 3425, 3340, 1645, 1585, and 1510 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) 1.47 (s, 9 H), 2.33 (s, 3 H), 2.37 (s, 3 H), and 6.8 (broad, 3 H, NH) ppm; mass spectrum, m/e 43, 137, 165 (100), and 238 (M^+).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.41; H, 7.73; N, 11.56.

The filtrate was acidified with 3 N HCl, causing a gum to separate. After stirring at room temperature for 4 days, this material was taken up in methylene chloride and chromatographed on 130 g of silica gel. Elution with methylene chloride gave compounds **19** and **20**. Recrystallization of the fractions rich in **19** from aqueous ethanol gave 1.15 g (5.2%) of 1-*tert*-butyl-2-hydroxy-3-acetyl-4-cyano-5-methylpyrrole (**19**). A sample recrystallized from aqueous ethanol had mp 83–85 °C: IR (Nujol) 3100, 2215, 1640, and 1570 cm^{-1}; NMR ($CDCl_3$) 1.62 (s, 9 H), 2.40 (s, 3 H), 2.50 (s, 3 H), and 13.4 (broad, OH) ppm; mass spectrum, m/e 57, 146, 164 (100), and 220 (M^+).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 64.68, H, 7.03; N, 12.47.

Recrystallization of the fractions rich in **20** from aqueous ethanol gave 450 mg (2.7%) of 2-hydroxy-3-acetyl-4-cyano-5-methylfuran as colorless crystals with mp 130–132 °C (a diamorph with mp 148–150 °C was also obtained): IR ($CHCl_3$) 3100 (broad), 2230, 1725, and 1635 cm^{-1}; NMR ($CDCl_3$) 2.33 (s, 3 H), 2.38 (s, 3 H), and 10.97 (s, OH) ppm; mass spectrum, m/e 43 (100) and 165 (M^+).

Anal. Calcd for $C_8H_7NO_3$: C, 58.19; H, 4.27; N, 8.48. Found: C, 58.14; H, 4.36; N, 8.58.

Further elution of the column gave a viscous syrupy material.

***N,N*-Dimethyl-2-chloroacetoacetamide (21).** Diketene (42 g, 0.5 mol) was mixed with ice and water (200 mL) and treated with 25% aqueous dimethylamine (90 mL). On completion of the addition, the solution was allowed to warm to room temperature and stirred for 30 min. It was then cooled with an ice bath, acidified with concentrated HCl (250 mL), and treated with aqueous sodium hypochlorite ("Chlorox"; 800 mL) by rapid dropwise addition. After warming to room temperature, the resulting mixture was extracted three times with 400-mL portions of methylene chloride. After drying and evaporation of solvent, the product was vacuum distilled to give 67.65 g (83%) of pale yellow liquid with bp 97–98 °C (0.05 mm): IR (film) 1730 and 1645 cm^{-1}; NMR ($CDCl_3$) 2.40 (s, 3 H), 3.03 (s, 3 H), 3.20 (s, 3 H), and 5.30 (s, 1 H) ppm; mass spectrum, *m/e* 43 and 163 (M^+).

Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16, Cl, 21.67; N, 8.56. Found: C, 44.31; H, 6.29, Cl, 21.73; N, 8.66.

2-Hydroxy-3-acetyl-4-cyano-5-methylfuran (20). A solution of compound **21** (3.28 g, 0.02 mol) in methanol (10 mL) was treated with the sodium enolate of cyanoacetone (2.1 g, 0.02 mol) and heated on a steam bath for 10 min. It was then cooled and acidified with 3 N HCl. After standing at room temperature for 20 h, the crystals of **20** were collected, washed with cold water, and air-dried. This crop of 2 g, together with a second crop, gave 2.2 g (66.7%) of the higher melting diamorph with mp 148–150 °C. Identity with the sample obtained previously was established by IR and mass spectra and TLC.

Crystallography. Crystals of compound **4** for structure analysis were grown from aqueous ethanol. The crystal data were as follows: space group Ia; a = 7.488 Å; b = 15.297 Å; c = 7.071 Å; β = 97.05°; Z = 4; d_{calcd} = 1.356 g/cm^3; and μ (Cu Kα) = 8.5 cm^{-1}.

The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation; θ–2θ scans; pulse height discrimination). The size of the crystal used for data collection was approximately 0.05 × 0.08 × 0.45 mm; the data were not corrected for absorption. Of the 822 accessible reflections for $\theta < 76°$, 638 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[8] and refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.040 and R_w = 0.038 for the 638 observed reflections. The final difference map had no peaks greater than ±0.2 eA^{-3}.

The C–N and C=O bond lengths of the amino and ketone functions, assumed on the basis of the very weak basicity of **4** to be involved in a resonance interaction, are 1.32 and 1.23 Å, respectively.

Acknowledgment. The interest and suggestions provided by Dr. Willy Leimgruber are greatly appreciated.

Registry No.—**1**, 5765-44-6; **2**, 7064-36-0; **3** ketone form, 60930-76-9; **3** enol form, 67271-59-4; **4**, 67271-60-7; **6**, 67271-61-8; **7**, 609-15-4; **8**, 1694-29-7; **9**, 67271-62-9; **10**, 67271-63-0; **11**,67271-64-1; **12**, 67271-65-2; **13**, 4439-88-7; **14**, 67271-66-3; **15**, 67271-67-4; **16**, 67271-81-2; **17**, 67271-68-5; **18**, 67271-69-6; **19**, 67271-70-9; **20**, 67271-71-0; **21**, 5810-11-7; cyanoacetone sodium enolate, 67271-72-1; ammonia, 7664-41-7; diketene, 674-82-8; *tert*-butylamine, 75-64-9; dimethylamine,124-40-3.

Supplementary Material Available: Final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles of **4** (Tables I–IV, respectively) (2 pages). Ordering information is given on any current masthead page.

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Cyclic Sulfamides: Synthesis of Some Fused Tetrahydrobenzo- and Tetra- and Dihydroheterothiadiazinone 2,2-Dioxides[1]

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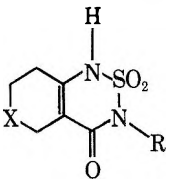
General methods for the synthesis of the title compounds (**1–3**) are described. The two key steps in these syntheses are the regiospecific sulfamoylation of primary enamino esters **9** and an acid-catalyzed ring closure procedure which offers distinct advantages over existing methods. Thus, the title compounds bearing bulky alkyl groups on N-3 are available in high yield from available β-keto esters.

In 1962 Cohen and Klarberg reported a new class of fused ring sulfamides, the 2,1,3-benzothiadiazin-4-one 2,2-dioxides.[2] The subsequent discovery that certain alkylated derivatives of this class of compounds possess uniquely selective phytotoxic properties[3] has made further synthesis in this area a relevent problem. This paper details general methods for the synthesis of some reduced and heterosubstituted reduced forms of these fused ring cyclic sulfamides, including the 5,6,7,8-tetrahydro-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxides **1**, the dihydro-2,1,3-thiopyranothiadiazin-4-one 2,2-dioxides **2**, and the tetrahydro-2,1,3-pyridothiadiazin-4-one 2,2-dioxides **3**.

Our initial synthetic efforts in this area involved attempted direct formation of the desired ring system by condensation



1, X = CH_2
2, X = S
3, X = N–R′

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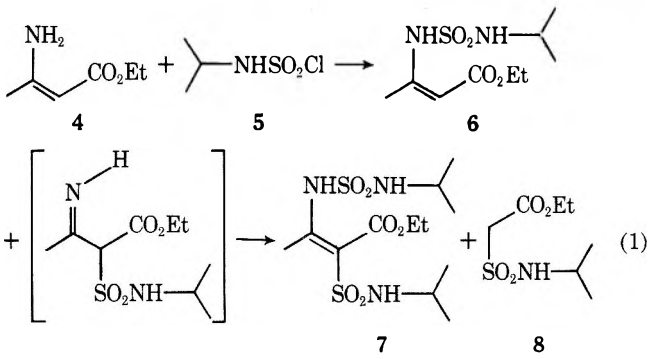
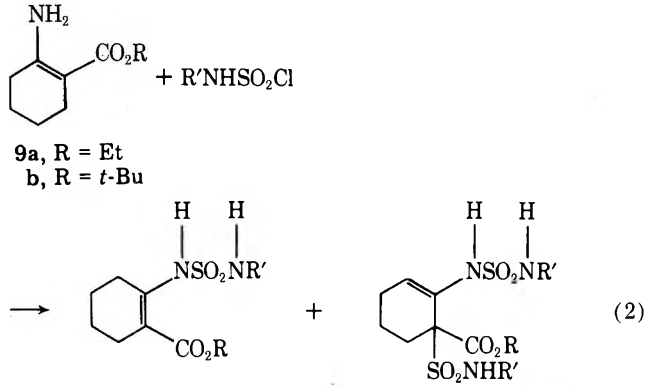
of sulfamide with a β-keto ester. Although such a condensation succeeds with β-diketones,[4] it failed in this case. We therefore adopted a two-step approach conceptually similar to that employed by Cohen and Klarberg,[2] namely, sulfamoylation of a primary β-enamino ester followed by ring closure. To test the potential of this proposed route, a model study was undertaken using ethyl 3-aminocrotonate (**4**) and *N*-isopropylsulfamoyl chloride (**5**).[5] These results are shown in eq 1. Reaction of **4** with **5** in the presence of triethylamine gave rise to the three products shown (**6**, **7**, and **8**) in a ratio of 1:2:3.5. Compounds **7** and **8** could reasonably arise from the common intermediate shown. In this model case, amino crotonate **4**, an ambident nucleophile, was showing a decided preference to react at the α carbon rather than at the nitrogen.



4 **5** **6** **7** **8** (1)

This result was not overly discouraging for it was expected that in the synthesis of the desired bicyclo compounds (**1**–**3**) the intermediates required (e.g., enamino esters **9**) would already bear substitution at the α carbon and that this substitution would promote reaction at nitrogen. Accordingly, the model system was abandoned and attention was focused on the cyclic β-enamino esters needed for the bicyclic compounds desired.

These enamino esters are available from the corresponding β-keto esters by a number of routes.[6] When **9a** was allowed to react with isopropylsulfamoyl chloride in the presence of triethylamine, the result was a 4:1 mixture of monosubstituted product **10a** to disubstituted **11** (eq 2). This dramatic shift in the ratio of N-substitution to C-substitution corroborated the expectation that partially blocking the β carbon would alter the course of the reaction.



9a, R = Et
b, R = *t*-Bu

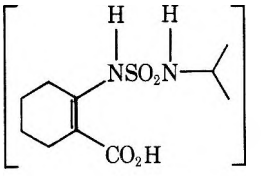
10a, R = C_2H_5; R′ = *i*-Pr **11**, R = C_2H_5; R′ = *i*-Pr
b, R = *t*-Bu; R′ = *i*-Pr (2)

Nevertheless, better ratios were needed for this to be a synthetically useful transformation. In the presence of a base, sulfamoyl chlorides are dehydrohalogenated to *N*-sulfonylamines,[7] which are then attacked by nucleophiles to give products. It was reasoned that the use of a base much weaker than triethylamine would increase the regioselectivity of the reaction by either lowering the concentration of *N*-sulfonylamine in solution or by allowing the reaction to proceed through a different mechanism. This reasoning proved sound, for when a second equivalent of enamino ester **9a** was employed in lieu of triethylamine, the only product isolated was sulfamoyl ester **10a**.

Having thus achieved regiospecificity in the sulfamoylation step, there remained only the task of cyclizing the intermediate sulfamoyl esters (**10**) to the desired compounds **1**. Cohen and Klarberg had employed aqueous base to cyclize their compound which was lacking alkyl substitution on nitrogen.[2] Compounds such as **10a**, wherein R′ is a primary alkyl group, cyclize equally well under these conditions. Dissolution in 5% aqueous sodium hydroxide followed shortly by precipitation with hydrochloric acid provided tetrahydrobenzothiadiazinones **1** (R = primary alkyl) in good yields. However, when R′ became a branched alkyl group such as isopropyl, yields for this procedure dropped precipitously. The starting material was consumed, and NMR spectra of the reaction residues suggested that a competing process was resulting in loss of the isopropyl group.

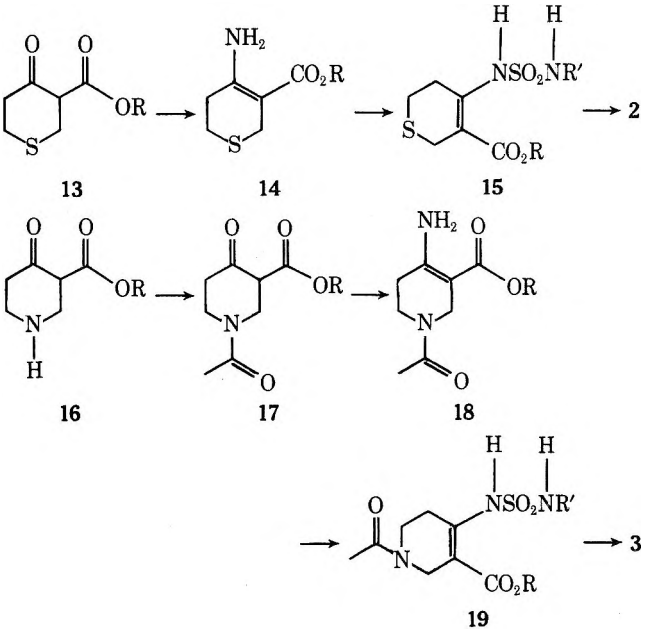
This result and those of other experiments aimed at ameliorating this problem suggested that a successful ring closure procedure would rely upon activation of the ester portion of the molecule rather than the sulfamide.

An attractive alternate intermediate therefore became *tert*-butylenamino ester **9b**.[6] This compound was sulfamoylated as described above to provide the sulfamoyl ester **10b**. Dissolution of this compound in 1:1 trifluoroacetic acid/trifluoroacetic anhydride for 10 min followed by evaporation of the solvents afforded the *N*-isopropyltetrahydrobenzothiadiazinone (**1**; R = *i*-Pr) in 89% yield. Presumably the strong acid effects cleavage of the ester to provide the sulfamoyl acid intermediate **12**, which then cyclizes, possibly via a mixed anhydride.



12

Methodology is therefore in hand for construction of a wide variety of tetrahydrobenzothiadiazinone 2,2-dioxides, with the only synthetic precursor being an available β-keto ester. To demonstrate the generality of this methodology, several examples of two new heterocyclic ring systems were synthesized using various combinations of the procedures described above. Keto esters of general structure **13**[8] were converted to



13 **14** **15** **16** **17** **18** **19**

the corresponding dihydro-2,1,3-thiopyranothiadiazin-4-one 2,2-dioxides **2**, while keto esters of gross structure **16**[9] gave rise to the tetrahydro-2,1,3-pyridothiadiazin-4-one 2,2-dioxides **3**. A detailed description of the preparation of a specific example of each of these ring systems [**2** (R = CH_3) from **13** (R = CH_3) and **3** (R = CH_3) from **16** (R = C_2H_5)] is included in the Experimental Section.

Experimental Section

General. Melting points were determined on a Laboratory Devices Melt-Temp apparatus and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on Varian T-60 and EM-360 spectrometers. Spectra were run using tetramethylsilane as an internal standard, and chemical shifts are reported in parts per million (ppm) downfield (δ) relative to Me_4Si = 0. Combustion analyses were performed by Atlantic Microlabs, Galbraith Laboratories, or the Monsanto Physical Sciences Center. Analytical thin-layer chromatography was performed using Baker-flex precoated silica gel slides.

Condensation of Ethyl 3-Aminocrotonate with *N*-Isopropylsulfamoyl Chloride. To a solution of 6.46 g (0.05 mol) of ethyl 3-aminocrotonate (**4**) and 7.8 g (0.05 mol) of *N*-isopropylsulfamoyl chloride in benzene was added 5.06 g (0.05 mol) of triethylamine. The resulting suspension was stirred at 50 °C for 24 h and cooled. The solution was washed with 2.5% hydrochloric acid and water, dried over magnesium sulfate, and concentrated to an oil. This oil was chromatographed on a silica gel column (10–50% ethyl acetate/cyclohexane) to afford three products. The first, ethyl 3-(*N*-isopropylsulfamoylamino)crotonate (**6**; 0.8 g, 7%), was isolated as an oil: NMR ($CDCl_3$) δ 1.20 (d, J = 6 Hz, 6 H), 1.22 (t, J = 8 Hz, 3 H), 2.15 (s, 3 H), 3.30–3.80 (m, 1 H), 4.20 (q, J = 8 Hz, 2 H), 4.95 (m, 1 H), 5.10 (broad d, J = 8 Hz, 1 H).

The second product, ethyl α-(*N*-isopropylsulfamoyl)acetate (**8**; 3.6 g, 34%), was isolated as an oil: bp 150 °C (0.05 mm); NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 6 H), 1.30 (t, J = 8 Hz, 3 H), 3.40–4.00 (m, 1 H), 4.05 (s, 2 H), 4.30 (q, J = 8 Hz, 2 H), 5.10 (broad d, 1 H).

Anal. Calcd for $C_7H_{15}NO_4S$: C, 40.18; H, 7.23; N, 6.69. Found: C, 39.99; H, 7.31; N, 7.13.

The third product, ethyl *N*,2-bis(*N'*-isopropylsulfamoyl)-3-aminocrotonate (**7**; 3.6 g, 20%), was also an oil: NMR ($CDCl_3$) δ 1.20 (d, J = 6 Hz, 12 H), 1.22 (t, J = 6 Hz, 3 H), 2.45 (2 singlets, 3 H), 3.10–3.20 (m, 2 H), 4.00–4.50 (m, 2 H), 4.90–5.15 (broad, m, 2 H).

Condensation of Ethyl 2-Amino-1-cyclohexene-1-carboxylate (9a) and *N*-Isopropylsulfamoyl Chloride in the Presence of Triethylamine. To a solution of 8.45 g (0.05 mol) of β-enamino ester **9a** and 10.1 g (0.1 mol) of triethylamine in benzene at 10 °C was added dropwise 8.7 g (0.055 mol) of *N*-isopropylsulfamoyl chloride. When the addition was complete, the solution was stirred for 1 h, washed with water, dried over magnesium sulfate, and concentrated to a viscous oil. This oil was chromatographed on a silica gel "dry column" (20% ethyl acetate/cyclohexane) to afford two products. The first of these, ethyl *N*-(*N'*-isopropylsulfamoyl)-2-amino-1-cyclohexene-1-carboxylate (**10a**; 5.9 g, 41%), was isolated as an oil: NMR ($CDCl_3$) δ 1.2 (d, J = 6 Hz, 6 H), 1.22 (t, J = 8 Hz, 3 H), 1.50–2.90 (m, 8 H), 3.40–3.80 (m, 1 H), 4.25 (q, J = 8 Hz, 2 H), 4.65 (broad d, 1 H); IR (film) 1680 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_2O_4S$: C, 49.63; H, 7.64; N, 9.65. Found: C, 49.36; H, 7.76; N, 9.50.

The second product, ethyl 1,*N*-bis(*N'*-isopropylsulfamoyl)-2-amino-2-cyclohexene-1-carboxylate (**11**; 2.0 g, 10%), was isolated as a solid: mp 88–92 °C; NMR ($CDCl_3$) δ 1.2 (d, J = 6 Hz, 12 H), 1.22 (t, J = 8 Hz, 3 H), 1.50–2.80 (m, 6 H), 3.40–3.95 (m, 2 H), 4.35 (q, J = 8 Hz, 2 H), 4.80 (broad d, 1 H), 5.20 (broad d, 1 H), 6.10 (t, J = 4 Hz, 1 H), 6.95 (broad s, 1 H); IR (film) 1715 cm^{-1}.

Anal. Calcd for $C_{15}H_{29}N_3O_6S_2$: C, 43.78; H, 7.10; N, 10.21. Found: C, 44.06; H, 7.21; N, 10.08.

Also isolated was 3.6 g (42%) of 2-carbethoxycyclohexanone.

Condensation of 2-Amino-1-cyclohexene-1-carboxylates (9a and 9b) with Isopropylsulfamoyl Chloride in the Absence of Triethylamine. A solution of 2 equiv of β-enamino ester **9a** or **9b** in benzene was cooled to 5 °C and treated with 1 equiv of *N*-isopropylsulfamoyl chloride. The resulting solution was stirred for 48 h at room temperature, washed with water, dried over magnesium sulfate, and concentrated to afford the crude product.

Ethyl ester **10a** (see above) was isolated in 78% yield.

tert-Butyl ester **10b** was isolated in 73% yield: mp 97–99 °C (from pentane); NMR ($CDCl_3$) δ 1.20 (d, J = 6 Hz, 6 H), 1.55 (s, 9 H), 1.40–2.90 (m, 8 H), 3.40–3.90 (m, 1 H), 4.45 (broad d, 1 H).

Anal. Calcd for $C_{14}H_{26}N_2O_4S$: C, 52.80; H, 8.23; N, 8.80. Found: C, 52.68; H, 8.28; N, 8.71.

3-Isopropyl-5,6,7,8-tetrahydro-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-Dioxide (1; R = *i*-Pr). A solution of 0.75 g of sulfamoyl ester **10b** in 5 mL of trifluoroacetic acid and 5 mL of trifluoroacetic anhydride was stirred at room temperature for 5 min. The solvents were evaporated, and the resulting solid was triturated with hexane to provide 0.5 g (87%) of cyclic sulfamide **1** (R = *i*-Pr) as a solid: mp 188–192 °C; NMR ($CDCl_3$) δ 1.50 (d, J = 6 Hz, 6 H), 1.40–2.5 (m, 8 H), 4.60–5.20 (m, 1 H).

Anal. Calcd for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.47. Found: C, 49.19; H, 6.60; N, 11.42.

4-Amino-3-carbomethoxy-5,6-dihydro-2*H*-thiopyran (14). A solution of 52.75 g of 4-oxo-3-carbomethoxy-5,6-dihydro-2*H*-thiopyran (0.3 mol), 27 g of urethane (0.3 mol), and a catalytic amount of *p*-toluenesulfonic acid in 300 mL of benzene was refluxed for 20 h, using a Dean-Stark trap to separate water. The solution was cooled and the solvent evaporated to provide an oil. This oil was added to a solution of 35 g of sodium methoxide in 600 mL of methanol and refluxed under nitrogen for 18 h. The solution was then cooled and poured into 1200 mL of ice/water. This mixture was extracted five times with a total of 2 L of ether. These extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated to an oil. Distillation provided 28 g (54%) of enamino ester **14**: bp 124 °C (0.45 mm); NMR ($CDCl_3$) δ 2.40–3.00 (m, 4 H), 3.50 (s, 2 H), 3.80 (s, 3 H), 6.5 (broad, 2 H).

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; N, 8.09. Found: C, 48.60; H, 6.42; N, 8.18.

3-Methyl-7,8-dihydro-1*H*,5*H*-thiopyrano[3,4-*e*]-2,1,3-thiadiazin-4(3*H*)-one 2,2-Dioxide (2; R = CH_3). A solution of 4 g (23.1 mmol) of enamino ester **14** and 1.5 g (11.6 mmol) of *N*-methylsulfamoyl chloride in 60 mL of benzene was stirred for 18 h at room temperature under nitrogen. The solution was diluted with an equal volume of ether and washed two times with water. The organic fraction was then poured into 60 mL of 5% aqueous sodium hydroxide, and the resulting suspension was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was cooled in an ice bath. Acidification with concentrated hydrochloric acid precipitated 2 g (77%) of cyclic sulfamide **2** (R = CH_3) as a solid. Recrystallization from acetonitrile provided an anayltical sample: mp 205–207 °C dec; NMR (Me_2SO-d_6) δ 2.3–2.9 (m, 4 H), 3.1 (s, 3 H), 3.35 (s, 2 H).

Anal. Calcd for $C_7H_{10}N_2O_3S_2$: C, 35.88; H, 4.30; N, 11.96. Found: C, 35.89; H, 4.32; N, 12.03.

Ethyl *N*-Acetyl-4-oxopiperidine-3-carboxylate (17; R = C_2H_5). To a vigorously stirred suspension of 95 g (0.46 mol) of ethyl 4-oxopiperidine-3-carboxylate hydrochloride in 600 mL of benzene, cooled in an ice bath and under nitrogen, was added 101 g (1 mol) of triethylamine. Immediately following, 39.5 g (0.5 mol) of acetyl chloride was added dropwise. The resulting pasty suspension was stirred overnight, and the solids were filtered off. The filtrate was washed two times with water, dried over magnesium sulfate, and concentrated to a semisolid. This was taken up in a minimum amount of warm ether, pentane was added to the cloud point, and the solution was allowed to stand. Filtration provided 69 g (71%) of *N*-acetylpiperidine **17**: NMR ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 3 H), 2.10 (s, 3 H), 2.20–2.55 (m, 2 H), 3.40–4.50 (m, 6 H), 11.40 (s, 1 H). This crude product was satisfactory for use in the next step.

***N*-Acetyl-4-amino-3-carbomethoxy-1,2,5,6-tetrahydropyridine (18; R = CH_3).** A solution of 69 g (0.33 mol) of keto ester **17**, 29 g (0.33 mol) of urethane, and a catalytic amount of *p*-toluenesulfonic acid in 800 mL of benzene was refluxed for 18 h, using a Dean-Stark trap to remove water. The solution was cooled and concentrated to provide a solid. The solid was dissolved in a solution of 7.5 g of sodium methoxide in 700 mL of methanol and refluxed under nitrogen for 18 h. A major portion of the methanol was distilled out, and the residue was poured into 700 mL of brine. This was continuously extracted with ethyl acetate. The extracts were combined and concentrated to a solid. Recrystallization from toluene provided 30 g (58%) of enamino ester **18**: mp 138–140 °C; NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.10–2.55 (m, 2 H), 3.70 (s, 3 H), 3.35–3.80 (m, 2 H), 4.05–4.30 (m, 2 H), 6.00–6.80 (broad, 2 H).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.33; H, 7.12; N, 14.13. Found: C, 53.89; H, 7.18; N, 13.96.

6-Acetyl-3-methyl-5,6,7,8-tetrahydro-1*H*-pyrido[3,4-e]-2,1,3-thiadiazin-4(3*H*)-one 2,2-Dioxide (3; R = CH_3). A solution of 5 g (25.2 mmol) of enamino ester **18** and 1.63 g (12.6 mmol) of *N*-methylsulfamoyl chloride in 60 mL of benzene was stirred for 18 h under nitrogen. The solution was washed with water and then extracted with three 20-mL portions of 5% aqueous sodium hydroxide. These extracts were cooled in an ice bath and acidified with concentrated hydrochloric acid. Extraction with ethyl acetate followed by drying over magnesium sulfate and concentration provided 2 g of an

oil which crystallized from acetonitrile to provide 0.9 g (29%) of cyclic sulfamide **3** (R = CH_3): mp 199–201 °C; NMR ($CDCl_3$) δ 2.1 (s, 3 H, 2.20–2.65 (m, 2 H), 3.15 (s, 3 H), 3.65 (t, J = 6 Hz, 2 H), 4.15 (broad s, 2 H).

Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21. Found: C, 41.69; H, 5.08; N, 16.23.

Registry No.—**1** (R = *i*-Pr), 67210-12-2; **2** (R = CH_3), 67210-13-3; **3** (R = CH_3), 67210-14-4; **4**, 7318-00-5; **5**, 26118-67-2; **6**, 67210-15-5; **7**, 67210-16-6; **8**, 67210-17-7; **9a**, 1128-00-3; **9b**, 65277-17-0; **10a**, 67210-18-8; **10b**, 67210-19-9; **11**, 67210-20-2; **13** (R = CH_3), 4160-61-6; **14** (R = CH_3), 67210-21-3; **16** (R = C_2H_5) HCl, 4644-61-5; **17** (R = C_2H_5), 4451-85-8; **18** (R = CH_3), 67210-22-4; 2-carbethoxycyclohexanone, 1655-07-8; urethane, 51-79-6; *N*-methylsulfamoyl chloride, 10438-96-7.

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Sulfoxides, Sulfilimines, Methoxysulfonium Salts, and Sulfoximines Derived from 3-Methyl-3-phenylthietane[1]

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3-Methyl-3-phenylthietane (**1**), 3-isopropyl-3-phenylthietane (**10**), 3-(*p*-bromophenyl)-3-methylthietane (**11**), 2-thiaspiro[3.5]nonane (**12**), 2-thiaspiro[3.5]non-6-ene (**13**), 3-methyl-3-nitrothietane (**14**), 5-methyl-2-thiaspiro[3.5]nonane (**15**), 6-methyl-2-thiaspiro[3.5]nonane (**16**), and 7-methyl-2-thiaspiro[3.5]nonane (**17**) were prepared by treating the corresponding 2,2-disubstituted 1,2-trimethylene bis(benzenesulfonates) with sodium sulfide in dimethyl sulfoxide. Oxidation of **1** by hydrogen peroxide or by sodium hypochlorite gave 3-methyl-*t*-3-phenylthietane *r*-1-oxide (**2**) and 3-methyl-*c*-3-phenylthietane *r*-1-oxide (**3**). Configurations were determined by NMR spectroscopy. Thermal interconversion of **2** and **3** proceeds at rates comparable to acyclic analogues and much slower than the rate reported for 3-*tert*-butylthietane 1-oxide. Relative rates of reaction of water and hydroxide ion at sulfur and methyl carbon in the hydrolysis of the diastereomeric methoxysulfonium salts derived from **2** and **3** were determined. Mass spectra of 2,2,4,4-tetradeuterated derivatives of **1**, **2**, **3**, and 3-methyl-3-phenylthietane 1,1-dioxide (**18**) were obtained. Sulfoxides **2** and **3** showed no differences in their mass spectra. An improved synthesis of *N*-*p*-toluenesulfilimines by the reaction of sulfides with anhydrous Chloramine-T–dimethylformamide solutions was used to synthesize 3-methyl-*c*-3-phenylthietane-*r*-*N*-(*p*-toluenesulfonyl)sulfilimine (**6**) and its diastereomer (**7**). Their rates of interconversion measured at 165 °C were somewhat slower than that for an acyclic arylalkyl analogue, but faster than that for an acyclic dialkyl *N*-acylsulfilimine. Silver ion formed complexes with sulfilimines with bonding at the N atom.

Thietanes and their S-substituted derivatives have been investigated extensively in recent years, but no 3-alkyl-3-arylthietanes or derivatives are included in these studies.[3–8] In fact, we found no mention of such compounds in the literature at all. We have synthesized 3-methyl-3-phenylthietane (**1**), converted it to diastereomeric sulfoxides **2** and **3**, methoxysulfonium salts **4** and **5**, sulfilimines **6** and **7**, and sulfoximines **8** and **9**, assigned configurations to these derivatives, determined the equilibrium between **2** and **3** and between **6** and **7**, and also studied some additional chemistry of these and related compounds. Our results and their relationship to previous investigations of various sulfoxides, sulfilimines, and sulfoximines, especially cyclic analogues, are described below.

	A	B	X	Y
1	Ph	Me	–	–
2	Ph	Me	–	O
3	Me	Ph	–	O
6	Me	Ph	–	NTs
7	Ph	Me	–	NTs
8	Me	Ph	O	NTs
9	Ph	Me	O	NTs
18	Ph	Me	O	O

Results and Discussion

3-Methyl-3-phenylthietane 1-Oxides (2 and 3). Thietane 1-oxides are prepared by oxidation of thietanes which are obtained most often through ring closure of 1,3-dibromides or 1,3-disulfonate esters[3,10,11] by sulfide ion, through fusion of cyclic carbonate esters of 1,3-diols with thiocyanate ion,[4,9] or by reduction of thietane 1,1-dioxides obtained by the cycloaddition of enamines with sulfene ($CH_2{=}SO_2$).[12–17] But 3-alkyl-3-arylthietanes and their derivatives had not been synthesized prior to our work; in fact, an attempt to prepare 3-ethyl-3-phenylthietane via the cyclic carbonate had failed.[18] Our preparation of 3-methyl-3-phenylthietane (**1**) was achieved by treatment of 2-methyl-2-phenyltrimethylene bis(benzensulfonate) with sodium sulfide in dimethyl sulfoxide. This modification of a standard thietane synthesis was also successful in preparing 3-isopropyl-3-phenylthietane (**10**) as well as the other 3,3-disubstituted thietanes (**11–17**) listed in Table I. In the two cases where comparisons are possible,

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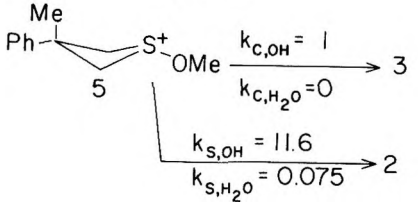
Table I. Thietanes Prepared from Benzenesulfonate Esters of 1,3-Diols

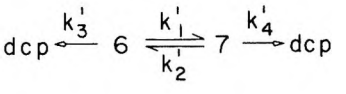
compd	thietane	yield, %	reaction time, h	bp, °C (mm)	sulfone registry no.	sulfone mp,[k] °C	benzenesulfonate registry no.	benzenesulfonate mp, °C	NMR, δ 3,3 substituent	NMR, δ α protons
1	3-methyl-3-phenyl-thietane	65	2	115–117 (12)	66809-99-2	54–55	66810-41-1	133.5–134.5	1.77 (s, 3 H)[h]	2.99 (d, 2 H, J = 9 Hz)
									7.21 (m, 5 H)	3.78 (d, 2 H, J = 9 Hz)
10	3-isopropyl-3-phenyl-thietane	22 (58)[a]	1	142–154 (10)	66810-33-1	89–90.5	66810-42-2	93.5–94.5	0.77 (d, 6 H, J = 7 Hz)[h]	3.27 (d, 2 H, J = 9.5 Hz)
									2.50 (sept, 1 H, J = 7 Hz)	3.62 (d, 2 H, J = 9.5 Hz)
									7.15 (m, 5 H)	
11	3-(*p*-bromophenyl)-3-methylthietane	66	3	56–57 (mp)	66810-34-2	137–138.5	66810-08-0	133.5–134.5	1.74 (s, 3 H)[i]	2.93 (d, 2 H, J = 9 Hz)
									7.19 (2d, 4 H)	3.55 (d, 2 H, J = 9 Hz)
12	2-thiaspiro[3.5]nonane	75 (26,[b] 42,[c] 57[d])	2	82–84 (7)	66810-35-3	71.5–72.5	2658-61-9	101–102	1.20–1.87 (m, 10 H)[i]	2.83 (s, 4 H)
				89–90 (13)[d]		72.5–73[b]		101–102[e]		
13	2-thiaspiro[3.5]non-6-ene	67 (34)[f]	7	111–115 (32)	66810-36-4	110.5–111.5	66810-09-1	103–104	1.63–2.58 (m, 6 H)[h]	2.63 (d, 2 H, J = 8 Hz)
									5.63 (m, 2 H)	2.80 (d, 2 H, J = 8 Hz)
14	3-methyl-3-nitro-thietane	41	2	101–102 (27)	66810-37-5	118–119	66810-10-4	112.5–114	1.98 (s, 3 H)[j]	3.17 (d, 2 H, J = 10 Hz)
								114[g]		4.03 (d, 2 H, J = 10 Hz)
15	5-methyl-2-thi-aspiro[3.5]nonane	48	42	93–95 (7)	66810-38-6	44–45.5	66810-11-5	89–90	0.83–2.27 (m 12 H)[i]	2.45–3.17 (m, 4 H)
16	6-methyl-2-thi-aspiro[3.5]nonane	64	14	92–94 (7)	66810-39-7	66–67	66810-12-6	76–78	0.68–2.40 (m, 12 H)[j]	2.78 (s, 2 H)
										2.83 (s, 2 H)
17	7-methyl-2-thi-aspiro[3.5]nonane	48	49	88–93 (7)	66810-40-0	67–68	66810-13-7	100–101	0.66–2.37 (m, 12 H)[h]	2.85 (s, 2 H)
										2.92 (s, 2 H)

[a] Obtained using anhydrous conditions (see Experimental Section). [b] H. J. Backer and A. F. Tamsma, *Recl. Trav. Chim. Pays-Bas*, **57**, 1183 (1938); from diol via the dibromide. [c] Reference 18. [d] Reference 11. [e] L. Shotte, *Ark. Kemi*, **9**, 309 (1956). [f] Prepared using the cyclic carbonate method of ref. 18. [g] J. L. Riebsomer, *J. Org. Chem.*, **11**, 182 (1946). [h] $CDCl_3$. [i] CCL_4. [j] Neat. [k] Thietanes were coverted to sulfones, which analyzed for carbon and hydrogen within 0.3% of theory.

Scheme I



Scheme II



higher yields, based on the common 1,3-diol precursors, were obtained using this procedure, e.g., 2-thiaspiro[3.5]nonane (**12**) was obtained in 26% yield from the dibromide, 42% from the cyclic carbonate, and 56% from the bis(benzenesulfonate) in ethylene glycol; our modification using the latter in dimethyl sulfoxide gave 75%. In our hands, 2-thiaspiro[3.5]-6-nonene (**13**) was formed in 34% yield via the cyclic carbonate method, while the bis(benzenesulfonate) procedure gave 67%.

The various thietanes were prepared by stirring the corresponding 1,3-bis(benzenesulfonate) esters with sodium sulfide nonahydrate in dimethyl sulfoxide at temperatures below 100 °C. Some of the reactions proceeded exothermically, whereas others needed prolonged heating on the steam bath to complete the reaction (see Table I). Product isolation was usually accomplished by extraction of the nonpolar thietanes into pentane from the water-diluted reaction mixtures. Distillation of the concentrated pentane extracts gave the thietanes in a high state of purity. The use of Me_2SO solutions of sodium sulfide from which most of the water had been removed by azeotropic distillation gave a dramatic increase in the yield of 3-phenyl-3-isopropylthietane (**10**) when compared to the untreated nonahydrate reaction yields, but it did not seem to affect the yield of 3-methyl-3-phenylthietane (**1**). Apparently, the yield of **10** was increased at the expense of the corresponding oxetane, formed in the reactions with the sodium sulfide nonahydrate.

Other compounds produced and identified by their spectral data were α-methylstyrene and 3-methyl-3-phenyloxetane in the reaction to form **1** and α-isopropylstyrene and 3-isopropyl-3-phenyloxetane in the reaction to form **10**. The other distilled thietanes (without an aromatic substituent), especially those whose production required long reaction times, showed up to 5% of an impurity by GLC analysis, which probably corresponded to the oxetane. Searles et al. also observed oxetane formation and fragmentation to olefins in the carbonate ester fusions.[18] Water- and pentane-insoluble gums, as well as nonvolatile but pentane-soluble products, were also present in our reactions.

Characterization of 3-methyl-3-phenylthietane (**1**) was accomplished by NMR spectroscopy and by oxidation to sulfone **18**, which gave an NMR spectrum and C,H analysis consistent with the proposed structure. Reduction of sulfone **18** by lithium aluminum hydride regenerated thietane **1**.

Diastereomeric 3-methyl-3-phenylthietane 1-oxides (**2** and **3**), obtained through oxidation of thietane **1** by hydrogen peroxide in acetic acid, were formed, without accompanying sulfone, in a ratio of 34:66 for **2/3**, isolated by distillation in 87% yield, and separated from one another by crystallization and column chromatography.

Assignment of Configuration to 2 and 3. Configurations as well as predominant conformations, were deduced mainly from the ^1H NMR spectra of **2** and **3**, in particular, from the resonances of the four thietane ring hydrogens which form an AA'BB' spin system. For sulfoxide **2** these α-methylene hydrogens gave rise to two very sharp multiplets, each consisting of eight resolved peaks, symmetrically disposed about a mirror plane separating them. The other sulfoxide, **3**, also gave rise to two multiplets. Although the low-field multiplet was sharp and resembled very closely the half-spectrum of **2**, the high-field multiplet was broadened due to long range coupling, as verified by decoupling experiments, between axial α- and 3-methyl protons, the latter appearing as a triplet.[7,19] One highly predominant conformation for **2** is consistent with the sharpness of its AA' and BB' multiplets, especially since thietane **1** and sulfone **18**, which are expected to be undergoing rapid ring inversion between two folded-ring conformations, both have one-half of their ring proton spectra broadened.

Microwave spectroscopy shows that thietane 1-oxide in the gas phase prefers the folded-ring conformation with the sulfinyl oxygen equatorial.[20] Both *cis*- and *trans*-3-(*p*-bromophenyl)thietane 1-oxides have similar conformations in the solid state,[21] as does a lanthanide complex of 3,3-dimethylthietane 1-oxide.[7] Solution conformations, while not as rigorously defined, also prefer equatorial rather than axial oxygen.[10b,22]

If the sulfinyl oxygen is equatorial, then **2** and **3** must have the configurations shown in the stereoformulas; this follows from the axial hydrogen axial methyl coupling predicted for and exhibited by **3** and not predicted for and absent in **2**.

Aromatic solvent induced shifts (ASIS), frequently used to assign configurations to cyclic sulfoxides,[13,24,25] are consistent with these stereochemical assignments. Benzene, thought to form a collision complex with the positive sulfur of the S–O dipole, shields the equatorial protons of **3** which must be closest to the complexed aromatic ring if the oxygen is equatorial and shifts their signals upfield relative to their signals in chloroform solution. The broadened, methyl-coupled, axial proton signals of **3** were shifted only 0.29 ppm compared to 0.72 ppm for the equatorial proton signals. In **2**, the axial protons should resonate upfield since they are anti to the sulfur lone pair of the equatorial sulfinyl group. Consistent with this, they undergo only a 0.44 ppm ASIS compared to 0.60 ppm for their equatorial counterparts. Had the sulfinyl oxygen been axial, the ASIS differences between protons should have been less pronounced.

In addition, the protons of the presumed axial 3-methyl group of **3** appear upfield (δ 1.47) compared to the equatorial methyl protons in **2** (δ 1.65). Since the sulfinyl bond shields groups which lie directly behind it along the S–O axis,[10b] this relative order of shifts agrees with the configurational assignments made to **2** and **3** with both molecules existing with the sulfinyl group predominantly equatorial.

Finally, an analysis of the NMR spectra of **2** and **3** measured in the presence of lanthanide chemical shift reagents supports the above assignments and not the reverse.[22]

Equilibration of 2 and 3. Sulfoxides **2** and **3** were equilibrated in chloroform and in dioxane by adding small amounts of hydrochloric acid to the solutions.[26,27] In chloroform the equilibrium ratio of **2** to **3** was 26:74; in dioxane the ratio was 29:71.

Thermal equilibration of **2** and **3** proceeded very slowly at 183 °C; e.g., after 1.4 h **3** did not form any detectable amount of **2**. Decomposition prevented measurements at higher temperature. These results contrast sharply with those obtained by Johnson[25] for the isomeric 3-*tert*-butylthietane 1-oxides which equilbrated in 15 min at 170–175 °C to a 85:15 cis/trans mixture;[27] the hydrochloric acid equilibration at 25 °C also gave this ratio. The integrated rate equation for the interconversion of **2** and **3** is shown by eq 1, where k_1 and k_2 are the rate constants for the forward and reverse reactions, K is the equilibrium constant, and the quantities in brackets are the concentrations of **2** and **3** at times 0 and t. Using a value of K based on the HCl-induced equilibrations and the concentrations of **2** and **3** after short periods of heating and before decomposition was judged serious, values of $k_1 + k_2 = 0.35 \times 10^{-5}$ s^{-1} at 164 °C and 1.8×10^{-4} s^{-1} at 201 °C were obtained. Extrapolation of the 164 °C value to 200 °C, using a fivefold rate increase per 20 °C as found by Mislow and coworkers[28] for acyclic sulfoxides, gave 8×10^{-5} s^{-1}. Mislow obtained constants of a similar magnitude: e.g., 1.4×10^{-5} s^{-1} for the racemization of phenyl *p*-tolyl sulfoxide at 200 °C and 1.2×10^{-5} s^{-1} for 1-adamantyl methyl sulfoxide at 210 °C. Our approximate approach to $k_1 + k_2$ suggests that sulfoxides **2** and **3** are similar to the various acyclic sulfoxides with respect to the rates of thermally induced pyramidal inversion at sulfur. The facile isomerization of 3-*tert*-butylthietane 1-oxide is puzzling and resembles the benzylic and allylic sulfoxide cases, where processes other than pyramidal inversion are

believed to be the cause of racemization.[29,30]

$$\ln \frac{[2]K - [3]}{[2^0]K - [3^0]} = -(k_1 + k_2)t \quad (1)$$

Oxidation of 1 to 2 and 3. Johnson and co-workers have studied the stereochemistry of the oxidation of various cyclic sulfides, including 3-substituted thietanes.[15,23] We used hydrogen peroxide and sodium hypochlorite as oxidants to prepare sulfoxides **2** and **3** from thietane **1**. Hydrogen peroxide yielded 66% of the thermodynamically most stable isomer, **3**, compared to 34% of **2**, but sodium hypochlorite gave 39% of **3** and 48% of **2** together with 13% of sulfone **18**. If thietane **1** exists principally in the folded conformation with the methyl axial, an assumption based on the smaller ΔG value for a methyl compared to a phenyl in cyclohexane systems[31] and on the broadening of the axial methyl proton NMR signal, then the peroxide appears to approach the sulfur atom preferentially along the least sterically hindered equatorial direction (steric approach control[15]). A more hindered axial approach involving the less likely conformation of **1** would also yield **3**, but if this argument is correct such a path should be of minor importance. To be self consistent, this description of the oxidation process then requires formation of **2** from the less stable conformer of **1** also by equatorial approach of the oxidant.

An explanation accounting for the greater amount of **2** compared to **3** formed when sodium hypochlorite is the oxidant follows similar lines.[15,23] A chlorosulfonium ion, R_2SCl^+, could be formed by equatorial attack of positive halogen on the preferred conformation of **1**. Sulfoxide **2** would result when chloride ion is displaced by an oxygen nucleophile such as water with inversion of configuration.[5] Since the reaction mechanism is not known with certainty, other speculative explanations are possible. The description just given has the virtue of being consistent with our interpretation of the peroxide oxidation results.

Johnson and co-workers found that hydrogen peroxide oxidation of 3-substituted thietanes gave predominantly the trans sulfoxides (axial oxygen and equatorial 3 substituent) rather than the thermodynamically more stable cis isomers (both substituents equatorial).[15] Apparently the 3-methyl substituent in **1** reverses the ease of approach to the diastereotopic faces of the sulfur atom relative to the 3-H in Johnson's thietanes.

Synthesis and Hydrolysis of Methoxysulfonium Salts 4 and 5. O-Methylation of sulfoxides **2** and **3** using trimethyloxonium tetrafluoroborate gave analytically pure samples of methoxysulfonium salts of retained configuration: **2** gave **4**, and **3** gave **5**. Alkaline hydrolysis of each salt produced sulfoxide with predominant inversion of configuration; some retention was always observed. Johnson has proposed that retention occurs by a competing S_N2 displacement on the alkoxy carbon with consequent C–O bond cleavage.[32] This proposal is supported by ^{18}O labeling studies.[33] Pseudorotation at sulfur, which might lead to overall retention of configuration, is thought not to occur.[34]

Solutions of the pure salts, either **4** or **5**, in tetramethylene sulfone (about 2 mL) were injected into a large volume (50–100 mL) of vigorously stirred, standardized sodium hydroxide solution which contained, whenever possible, a large stoichiometric excess of base. The amount of sulfoxide with retained configuration at sulfur increased monotonically with increasing base concentration to reach about 8% content at the highest base concentration used (4.6 N). Hydrolysis of the salts in pure water gave only the sulfoxide with inverted configuration. These results suggest that the sulfoxides with retained configurations arise from an attack of hydroxide ion on the *O*-methyl carbon atom. Pseudorotation of the tetracoordinate intermediate to give some sulfoxide with retained configuration would not be expected to show a dependence on the base concentration.

An analysis is shown for **5** in Scheme I; an analogous analysis is applicable for salt **4**. The rate expressions for this system, assumed to be those for typical second-order rate processes with a first-order dependence upon the salt concentration, the hydroxide ion concentration, and the water concentration, could be solved under the assumptions that the hydroxide ion concentration remained approximately constant during reaction (this was not strictly true for the second point, equivalent to a 0.0419 N NaOH solution, where the hydroxide ion concentration dropped about 35% in value) and that the rate constant for the attack of water on the *O*-methyl carbon was small enough to be neglected, that is, set equal to 0 inasmuch as no retention of configuration was observed in pure water. Solution of these equations showed that a plot of [sulfoxide, inverted]/[sulfoxide, retained] vs. $[H_2O]/[OH^-]$ should yield a straight line with a slope equal to $k_{S,H_2O}/k_{C,OH}$ and an intercept equal to $k_{S,OH}/k_{C,OH}$, where the k's are the second-order rate constants as shown in Scheme I. Good least-squares regression lines were obtained for both methoxysulfonium salts. The relative rate constants for **5** are summarized in Scheme I with $k_{C,OH} = 1$. The values obtained for **4** are $k_{C,H_2O} = 0$, $k_{C,OH} = 1$, $k_{S,H_2O} = 0.116$, and $k_{S,OH} = 10.4$.

Mass Spectra of 1, 2, 3, and 18. Fragmentation patterns elucidating the mass spectra of **1**, **2**, **3**, and **18** were proposed and corroborated by a comparison with the spectra of 2,2,4,4-tetradeuterated derivatives (**1**-*d*, **2**-*d*, **3**-*d*, and **18**-*d*).

Thietane **1** gave a molecular ion at *m/e* 164 (*m/e* 168 for **1**-*d*), a base peak at *m/e* 118 by loss of CH_2S (*m/e* 120 by loss of CD_2S for **1**-*d*), and a peak at *m/e* 103 by further loss of CH_3 (*m/e* 105 for **1**-*d*).

Sulfone **18** exhibited a fragmentation pattern similar to that of thietane **1**, except that the parent ion at *m/e* 196 lost CH_2SO_2 and CH_3SO_2 fragments (CD_2SO_2 and CD_3SO_2 for **18**-*d*) to give ions at *m/e* 118 and 117 (*m/e* 120 and 118 for **18**-*d*). Furthermore, loss of HSO_2 from **18** ocurred to give an ion at *m/e* 131 (*m/e* 135 for **18**-*d*); presumably the proton was abstracted from the 3-methyl group.

The fragmentation patterns of sulfoxides **2** and **3** were not distinguishable from one another. Apparently the molecular ions are equivalent. The patterns do differ somewhat from those observed for **1** and **18**. Loss of HSO gave a base peak at *m/e* 131 (*m/e* 134 for **2**-*d* and **3**-*d*) in contrast to the base peak at *m/e* 118 common to both **1** and **18** due to the loss of CH_2S and CH_2SO_2, respectively, but ions at *m/e* 118, 117, 115, 103, and 91 were found in common with **1** and **18**, although with different intensities. Neither **2** nor **3** appeared to abstract a proton from the 3-methyl as did sulfone **18**.

***N*-Tosyl-3-methyl-3-phenylthietane Sulfilimines 6 and 7.** Sulfilimines **6** and **7**, prepared from Chloramine-T in the usual way, were contaminated by the corresponding sulfoxides.[35] This is not uncommon, but results from water present in the solvent or in the usual commercial Chloramine-T which is a trihydrate. To avoid this diversion of the starting thietane, the water was removed from a dimethylformamide (DMF) solution of Chloramine-T by adding chlorobenzene followed by distillation under vacuum until DMF was the only component in the distillate. The residual bright greenish-yellow solution of the haloamide salt, judged to be an essentially anhydrous solution of Chloramine-T in DMF, had to be used within a few days of its preparation since it lost strength rather rapidly on storage. However, the slight amount of precipitate (assumed to be sodium chloride) that formed during its preparation implied that its formation was not accompanied by extensive decomposition.

The reaction of this solution with sulfides gave a dramatic

Table II. *N*-Tosylsulfilimines

compd	registry no.	sulfide precursor[l]	yield,[a] %	mp, °C	% isomer distribution[b]
20	53799-67-0	butyl methyl sulfide (19)	78,[c] 38,[d] 0[e]	89–90	
				89–90.5[f]	
22	10330-18-4	ethyl phenyl sulfide (21)	92,[c] 98,[d] 60[e]	98–99	
				97–98[g]	
6	66810-14-8	3-methyl-3-phenythietane (1)	95,[c] 74[d]	154–155	54.5 ± 2.5[h]
7	66810-15-9			114–115	45.5 ± 2.5[i]
23	66810-16-0	3-methyl-3-(*p*-bromophenyl)thietane (11)	98[c]	155.5–156.5	52.6 ± 0.5[h]
24	66810-17-1			159.5–160.5	47.4 ± 0.5[i]
25	66810-18-2	3-isopropyl-3-phenylthietane (10)	100[c]		42.7 ± 1.2
26	66810-19-3				57.3 ± 1.2
27	66810-20-6	3-methyl-3-nitrothietane (14)	93[c]		64.5 ± 1.2[j]
28	66810-21-7				34.6 ± 1.2[k]

[a] Isolated, base-washed product. [b] Determined by NMR. [c] Anhydrous Chloramine-T in DMF. [d] Chloramine-T trihydrate in DMF. [e] Chloramine-T trihydrate in pyridine. [f] M. A. McCall, D. S. Tarbell, and M. A. Harill, *J. Am. Chem. Soc.*, 73, 4476 (1951). [g] K. Tsujihara, N. Furakwa, and S. Oae, *Bull. Chem. Soc. Jpn.*, 43, 2153 (1970). [h] Aryl group and nitrogen are cis. [i] Aryl group and nitrogen are trans. [j] Nitro group and nitrogen are cis. [k] Nitro group and nitrogen are trans. [l] Registry no.: 19, 628-95-5; 21, 622-38-8.

increase in the yields of the crude isolated sulfilimines, formed practically quantitatively in many cases. The results are summarized in Table II. Even methyl butyl sulfide gave a 78% yield compared to 38% for its reaction with the Chloramine-T trihydrate in DMf. The data of Table II reveal the potential synthetic utility of the "anhydrous" reagent for the preparation of *N*-tosylsulfilimines from sulfides.[36,37]

N-Tosylsulfilimine pairs **6** and **7** and **23** and **24** were separated by tedious column chromatography on silica gel and then characterized by spectral and elemental analyses. Stereochemical assignments to **6** and **7** were made in the same way as for sulfoxides **2** and **3.** That is, **6** gave one methyl-coupled, broadened half-spectrum, the lower half in contrast to the sulfoxides, for the ring hydrogen absorptions, but **7** in benzene gave two sharp symmetrical halves. Thus, **6** and **7** have the configurations shown by the stereoformulas. Similar considerations permitted configurational assignments to be made to sulfilimines **23** and **24,** the *p*-bromophenyl group and nitrogen are cis in **23** and trans in **24.** Sulfilimines **6** and **23,** as well as sulfoxide **3,** all of the same configuration, migrated more rapidly over silica gel than did their corresponding isomers. Sulfilimines prepared from **10** and from **14** were not separated, although their NMR spectra (as mixed isomers) were entirely consistent with their proposed composition. NMR-based structural assignments to isomers **27** and **28** were accomplished by noting that the methyl signal of one of the isomers in the mixture was about twice as broad as the other methyl signal assigned to the other isomer. Therefore, the predominant isomer with the broadened methyl signal has the nitro group and nitrogen cis.

Sulfilimines **6** and **7** were oxidized to the corresponding sulfoximines with sodium permanganate, a reaction known to proceed with retention of configuration at the sulfur atom.[38,39]

Silver Complexes of Sulfilimines. The separation of the sulfilimines **6** and **7** was greatly facilitated by the discovery that **6** formed a slightly soluble molecular complex with silver nitrate while **7** remained in the supernatant solution. When a solution of sulfilimines **6** and **7** in a chloroform–benzene mixture was stirred with solid silver nitrate, a fine precipitate was deposited. Examination of the supernatant solution by NMR spectroscopy showed that it now contained isomer **7** in greater than 93% purity. Isomer **7** could be regenerated readily from the filtered solution by treatment with aqueous sodium chloride. A similar treatment of the insoluble precipitate gave **6.** Recrystallization of the recovered sulfilimines gave the pure isomers. However, isomer **6,** even after several recrystallizations, was unsuitable as the starting material for the thermal equilibrations described below because it decomposed on heating at a rate considerably faster than material which had not been treated with silver nitrate. Traces of silver nitrate in the sulfilimine probably caused this acceleration. Sufficient quantities of isomer **6** could be obtained free of **7** by crystallization without using the silver nitrate treatment. Isomer **7** did not show any difference in behavior dependent on whether the substance was obtained as above or by chromotography.

Attempts to crystallize **6**·$AgNO_3$ from methanol–toluene mixtures deposited crystals which at times were free of silver. This might be expected in relatively weak complexes. An infrared spectrum of **6**·$AgNO_3$, mechanically separated from the coarse silver nitrate crystals, was similar to the spectrum of the free sulfilimine **6,** but the strong S=N absorption[40] present at 970 cm^{-1} in **6** now appeared at 933 cm^{-1}. The material melted at 153–154 °C with strong darkening and evolution of brown fumes; the mp of **6** is 154–155 °C.

In order to circumvent these difficulties and still obtain additional data, *S*-ethyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)-sulfilimine (**22**) was chosen to serve as a model for the sulfilimine–silver nitrate adducts. The adduct of **22** and silver nitrate (**22**·$AgNO_3$) was somewhat more soluble than **6**·$AgNO_3$, and the formation of the complex was apparently much faster than its rate of crystallization, a fact which permitted separation of unchanged silver nitrate prior to the isolation of the adduct. Analysis (C,H,N) gave values agreeing very closely with a 1:1 ratio of **22** to silver nitrate. The melting point of **22**·$AgNO_3$ (130–131 °C) was quite different from the melting point of **22** (98–99 °C) or of silver nitrate (212 °C). The infrared spectrum of **22**·$AgNO_3$ showed that the S=N band was displaced from 972 cm^{-1} in **22** to 906 cm^{-1} in the adduct, although the rest of the spectrum remained similar to that of the free sulfilimine. The NMR spectrum of the complex showed striking differences from that of the free sulfilimine. Thus, the absorptions of **22**·$AgNO_3$ were shifted downfield with respect to the absorptions of **22;** the greatest effect was observed for the aromatic protons [δ(**22**·$AgNO_3$) − δ(**22**) = 0.27] and for the methylene group adjacent to the sulfur atom [δ(**22**·$AgNO_3$) − δ(**22**) = 0.38]. In addition, the methylene quartet of **22** now appeared as a multiplet, an indication that the accidental magnetic equivalence of the two diastereotopic protons had been removed. This latter effect could be greatly enhanced by the successive addition of benzene to the sample; the multiplet was finally separated into two distinct overlapping octets at δ 2.99 and at 3.17. Kucsman and co-workers[41] noted that benzene alone did not remove the accidental degeneracy of the diastereotopic methylene protons of **22,** an

observation consistent with our own observations.

It was quite surprising to realize that *N*-tosylsulfilimines formed adducts with silver nitrate because at the time there were no published reports of any metal–sulfilimine complexes. Examination of the NMR spectra of solutions of *N*-tosylsulfilimines and a lanthanide shift reagent led Nielsen and Kjaer[42] to conclude that no specific association existed between the nitrogen atom of the *N*-tosylsulfilimine and the lanthanide. However, complexes of palladium(II) and platinum(II) with *S,S*-dimethyl-*N*-benzoylsulfilimine (**29**) have been reported recently.[43] These authors concluded that the metal atom was coordinated to the nitrogen atom because the infrared frequency of the C=O bond was shifted to higher frequencies upon complexation with the metal. Unfortunately, these authors did not include a consideration of the S=N bond frequencies in their reports.

The infrared spectra of the adducts of *N*-tosylsulfilimines with silver(I) suggested that the metal atom in these compounds was also associated with the nitrogen atom. The shift of the S=N frequency to lower values in these adducts was analogous to the shifts observed in the sulfoxide–metal complexes bonded through the sulfinyl oxygen.[44,45] The NMR absorptions of **22**·$AgNO_3$ and the observed benzene-induced shifts in this compound also support this bonding situation in which the sulfur atom becomes more positive because of the complexation of the metal through the nitrogen atom.

Signals from both complexed and uncomplexed species of **29** were observed in the NMR spectra of the palladium complex.[43] This was not observed in the case of **22**·$AgNO_3$. These *N*-tosylsulfilimine complexes with the silver ion may probably best be regarded as the acid–base adducts of the "soft" Ag(I) acid with the substrate.[46]

Equilibration of Sulfilimines 6 and 7. Sulfilimines **6** and **7** could be thermally equilibrated. Samples of either isomer which had been heated longer than 45 min at 165 °C gave similar isomer distributions which were approximately independent of longer heating times. A competing decomposition, the extent of which varied between different runs, was a complicating factor. This decomposition introduced considerable scatter in the amount of sulfilimines not decomposed after each run and also affected the observed distributions of **6** and **7** in the samples. A consideration of the isomerization–decomposition process suggested that the sulfilimines isomerizations could be formally represented by Scheme II, which is mathematically equivalent to the two simultaneous first-order differential equations 2 and 3. The solution of this system of equations to give the rate constants k_1' and k_2' together with the equilibrium constant $K_{eq}' = k_1'/k_2'$ was obtained. The rate constants were $k_1' = (3.2 \pm 0.3) \times 10^{-4}\ s^{-1}$ and $k_2' = (4.8 \pm 0.2) \times 10^{-4}\ s^{-1}$ for the thermal isomerization of sulfilimines **6** and **7** at 165 °C. These values give $K_{eq}' = k_1'/k_2' = 0.667$; the equilibrium distribution of **6**/**7** at 165 °C is 60%: 40% with $\Delta G°_{165} = -0.353$ kcal/mol. The relative distributions of **6** and **7** (normalized to 100%) observed after equilibration times greater than 45 min were close to the equilibrium distributions of the isomers predicted by the kinetic data.

$$d[6]/dt = -(k_1' + k_3')[6] + k_2'[7] \quad (2)$$

$$d[7]/dt = k_1'[6] - (k_2' + k_4')[7] \quad (3)$$

Sulfilimine isomer **6** is configurationally analogous to the sulfoxide isomer **3**, and the equilibrium distributions of the sulfoxide and the sulfilimine isomers are consistent with a lower interaction between the 3 substituents of the thietane ring and the *N*-tosylimino group than between the same 3 substituents and the sulfinyl oxygen of the sulfoxides **2** and **3**. Experimental data on the conformational energies between the sulfinyl oxygen and the *N*-tosylimino group in the thiane system support this interpretation.[47]

The kinetics of the thermal isomerization of some optically active *N*-tosylsulfilimines[48] and *N*-acylsulfilimines[49] have been studied by other workers, who have proposed a pyramidal inversion mechanism for this process. The kinetic data obtained around 100 °C for *S*-methyl-*S*-(*p*-chlorophenyl)-*N*-(*p*-toluenesulfonyl)sulfilimine (**30**) gave a racemization rate constant of $2.2 \times 10^{-2}\ s^{-1}$ at 165 °C from a plot of ln *k* vs. 1/*T*.[48] Comparison of this value with the analogous isomerization rates of **6** and **7**, equivalent to $k_1' + k_2' = 8.0 \times 10^{-4}\ s^{-1}$, showed that the racemization of **30** was about 30 times faster. This difference may result from the aromatic *S*-(*p*-chlorophenyl) substituent of **30** absent in the thietane derivatives rather than CSC bond angle strain in the thietanes since the racemization rate of an *S,S*-dialkyl-*N*-acylsulfilimine was found to be much lower than the rates for **6**, **7**, and **30**.[49]

Experimental Section

General. Melting points were determined on a Hoover Uni-Melt capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 337 grating spectrometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 or a Jeolco HM-100 spectrometer with an internal tetramethylsilane standard. Coupling constants are in hertz and are apparent rather than true calculated values. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Microanalyses were carried out on an F and M Model 185 C,H,N analyzer or by Schwarzkopf Laboratories, Woodside, N.Y.[50] Thin-layer chromatography was performed on Brinkmann Polygram Sil S-HR/UV_{254} silica gel plates. Column chromatography was performed using Baker 60–200 mesh silical gel.

Thietanes. The preparation of **1** is given as representative of the other thietane syntheses, and the oxidation of **1** is given as representative of the sulfone preparations. However, hydrogen peroxide was used as the oxidant in the preparation of the sulfone derived from **13**. Water was removed in several cases from a Me_2SO–sodium sulfide nonahydrate solution by the addition of toluene followed by distillation of a toluene–water azeotrope from the mixture. All thietanes exhibited a characteristic infrared absorption band[18] at ca. 1175 cm^{-1}.

3-Methyl-3-phenylthietane (1). Freshly ground sodium sulfide nonahydrate (40.0 g, 0.17 mol) was added in one portion to crude 2-methyl-2-phenyltrimethylene bis(benzenesulfonate)[51] (205 g, 0.46 mol) in Me_2SO (400 mL). The mixture was stirred at ca. 90 °C for 2 h. Occasionally, 0.3-mL aliquots were removed and diluted with water. The absence of a crystalline precipitate after 2 h was taken to mean completion of the reaction. The cooled reaction mixture was poured into water and extracted with pentane, and the combined organic layers were washed with water, dried ($MgSO_4$), filtered, concentrated in vacuo, and distilled through a 15 cm Vigreux column to give **1**, 37.2 g. GLC indicated it to be 98% pure. Similar preparations gave yields from 49 to 64%.

Bis(benzenesulfonate) esters of propane-1,3-diols were prepared by the addition of benzenesulfonyl chloride (2.2–2.4 mol) to the diols (1.0 mol) dissolved in pyridine at 15 °C or lower. The mixtures were allowed to stand overnight at room temperature, and then they were poured into an ice–water mixture. The crude esters were removed by filtration and were converted directly to the thietane or else purified by recrystallization from a solvent such as carbon tetrachloride.

Propane-1,3-diols used to prepare thietanes **10**, **11**, and **16** were new compounds. 2-(*p*-Bromophenyl)-2-methylpropane-1,3-diol was prepared via the Tollens condensation[52] from *p*-bromohydratropaldehyde, formalin, and sodium hydroxide in aqueous ethanol in 77% yield: mp 86–87 °C; NMR ($CDCl_3$) δ 1.17 (s, 3 H, CH_3), 3.23 (s, 2 H, HO), 3.69 (q, 4 H, J = 11.0 Hz, CH_2), 7.3 (m, 4 H, C_6H_4). 2-Phenyl-2-isopropylpropane-1,3-diol was prepared by the lithium aluminum hydride reduction of the mixed ethyl and isopropyl esters of 2-isopropyl-2-phenylmalonic acid prepared by the treatment of diethyl phenylmalonate with 2-bromopropane and sodium in 2-propanol: overall yield, 21%, mp 56–57 °C; NMR (CCl_4) δ 0.70 (d, 6 H, J = 7.0 Hz, CH_3), 1.85 (heptet, 1 H, J = 7.0 Hz, CH), 3.83 (q, 4 H, J = 11.0 Hz, CH_2), 3.9 (s, 2 H, HO), 7.20 (s, 5 H, C_6H_5). 3-Methylcyclohexane-1,1-dimethanol was prepared via the Tollens condensation of 3-methycyclohexane-1-carboxaldehyde and formaldehyde in 25% yield: mp 72–73 °C; NMR ($CDCl_3$) δ 0.25–1.95 (m, 12 H, $C_6H_9CH_3$), 3.44 (s, 2 H, CH_2O), 3.73 (s, 2 H, CH_2O), 3.91 (s, 2 H, HO). The aldehyde was prepared via the Darzens glycidic ester condensation of 3-methycylohexanone and isoproypl chloroacetate and used without characterization.[52]

3-Methyl-3-phenylthietane 1,1-Dioxide (18). A 10% aqueous solution of sodium permanganate was added in small portions to a vigorously stirred mixture of thietane **1** (1.5 g, 9.1 mmol), acetic acid (1 mL), and water (5 mL). When the purple color persisted for at least 15 min, the reaction mixture was diluted with water and the excess permanganate and manganese dioxide were discharged with sodium bisulfite. The solids were collected by filtration and extracted with chloroform. The extract was dried over magnesium sulfate, filtered, and concentrated in vacuo to give **18**, which was recrystallized from benzene–cyclohexane: 61% yield; mp 54–55 °C; NMR ($CDCl_3$) δ 1.78 (s, 3 H, C–CH_3), 4.09 (d, 2 H, J = 12.5 Hz, S–CH), 4.48 (d, 2 H, J = 12.5 Hz, S–CH), 7.26 (m, 5 H, C_6H_5).

Reduction of 18 to 1. Lithium aluminum hydride (1.70 g, 0.0712 mol) in ether (50 mL) was added with stirring over 1 h to sulfone **18** (10.80 g, 0.0550 mol) in ether (100 mL)–benzene (25 mL). After 2 h, water (3 mL), 15% sodium hydroxide (3 mL), and water (9 mL) were added in that order. The solids were filtered and washed with ether. Concentration of the filtrate and ether washings gave an oil which upon distillation yielded thietane **1** (6.44 g, 71% yield), bp 120–122 °C (12 mm).

3-Methyl-3-phenylthietane 1-Oxides 2 and 3. Hydrogen peroxide (30%; 9.5 mL, 0.105 mol) in acetic acid (40 mL) was added to a stirred ice-cold solution of thietane **1** in acetic acid (60 mL). After 0.5 h at 0 °C and 2 h at room temperature, the mixture was concentrated in vacuo to give **2** and **3**. Integration of the two NMR methyl signals at δ 1.61 (34.0%) and 1.46 (66.0%) gave the ratio of **2/3**. Distillation gave a mixture of **2** and **3** unchanged in isomer ratio: 15.6 g (87% yield); bp 125–132 °C (0.2 mm). A carbon tetrachloride solution of this mixture was treated with heptane to yield crude **2**, which was recrystallized from cyclohexane to give 3.3 g: mp 88–89 °C; IR (KBr) 1058 cm^{-1} (SO); NMR ($CDCl_3$) δ 1.65 (s, 3 H, C–CH_3), 3.33 (d of t, 2 H, J = 12.5 Hz, S–CH_a), 4.08 (d ot t, 2 H, J = 12.5 Hz, S–CH_e), 7.07–7.62 (m, 5H, C_6H_5).

The residue (12.3 g) was chromatographed on 250 g of alumina to give crude **3**, which was furhter purified by vacuum distillation to yield 5.4 g: bp 117–120 °C (0.2 mm); IR (neat) 1071 cm^{-1} (SO); NMR ($CDCl_3$) δ 1.47 (s, 3 H, C–CH_3), 3.43 (broad d, 2 H, J = 11.0 Hz, S–CH_a), 3.86 (sharp d of t, 2 H, J = 11.0 Hz, S–CH_e), 7.00–7.62 (m, 5 H, C_6H_5) Irradiation at δ 1.47 caused the peak at δ 3.43 to sharpen and resemble the δ 3.86 resonance.

Reaction of 1 with Sodium Hypochlorite. Thietane **1** (2.46 g, 15.0 mmol) was added to an aqueous solution[53] of sodium hypochlorite (33.0 mL, 16.7 mmol) at ice-bath temperature. After 1 h, the mixture was extracted with methylene chloride several times to give an oil (2.65 g) consisting of **2** (47.8%), **3** (38.7%), and **18** (13.6%) as determined by NMR spectroscopy.

Thermal Equilibration of Sulfoxides 2 and 3. Individual samples of **2** and **3** in NMR tubes under nitrogen were heated in the vapors of boiling mesitylene (164 °C), *p*-bromotoluene (183 °C), acetophenone (201 °C), and *p*-methylacetophenone (223 °C). Sulfoxide **2** gave 7% of **3** after 8.0 h at 164 °C, 10% of **3** after 0.5 h at 201 °C (slight decomposition), and extensive decomposition after 0.25 h at 223 °C. Sulfoxide **3** gave no appreciable **2** after 1.4 h at 183 °C, 7% of **2** after 0.5 h at 201 °C (negligible decomposition), and complete decomposition after 0.5 h at 223 °C.

Chemical Equilibration of Sulfoxides 2 and 3. Four samples each of **2** and **3** (0.2–0.3 g) in a mixture of $CDCl_3$ (0.5 mL) and 37% hydrochloric acid (5 μL) were allowed to stand for 48 h. The isomer distribution was measured by NMR spectroscopy: **2**, 24.9 ± 0.5%; **3**, 75.1 ± 0.5%. Analysis of the combined equilibrated mixtures by TLC (Et_2O) gave spots for **2** and **3** only.

Two samples of **2** and **3** were also equilibrated in dioxane containing hydrochloric acid. The resulting equilibrium mixtures were analyzed by NMR spectroscopy and TLC: **2**, 28.9 ± 0.7%; **3**, 71.2 ± 1.0%. The validity of NMR analysis by integration of the methyl protons was checked using known mixtures of **2** and **3**.

1-Methoxy-3-methyl-3-phenylthietanium tetrafluoroborates 4 and 5 were prepared by treating sulfoxides **2** and **3** separately with a slight excess of trimethyloxonium tetrafluoroborate in methylene chloride. The mixtures were filtered, and ether was added to precipitate **4** and **5**, which then were recrystallized from chloroform or chloroform–carbon tetrachloride. Compound **4**: mp 113–115 °C; NMR ($CDCl_3$) δ 1.81 (s, 3 H, C–CH_3), 4.19 (s, O–CH_3), 4.19 and 4.78 (broad d of d, 4 H, J = 14.0 Hz, CH_2S), 7.31 (m, 5 H, C_6H_5). Compound **5**: mp 80–82 °C; NMR ($CDCl_3$) δ 1.74 (s, 3 H, C–CH_3), 4.23 (s, O–CH_3), 4.38 and 4.80 (broad d of d, 4 H, J = 13.4 Hz, CH_2S), 7.34 (m, 5 H, C_6H_5).

Reaction of 4 and 5 with Sodium Hydroxide. Aliquots (2.0 mL) of a solution (15.0 mL) of **4** (3.100 g, 10.99 mmol) in tetramethylene sulfone (sulfolane) were added in one portion to vigorously stirred aqueous solutions of sodium hydroxide of known normality. Five solutions of 50 mL each varying in normality from 0.307 to 4.58 N, one 100-mL solution of 0.0419 N, and pure water (100 mL) were used. After 1 h, the mixtures were extracted with methylene chloride to yield sulfoxides **2** and **3**. NMR analysis by integration of the 3-methyl signals gave the ratio of **2/3**. A least-squares regression analysis of [**3**]/[**12**] vs. $[H_2O]/[OH^-]$ gave a straight line with a slope of 0.16 ± 0.008, an intercept of 10.4 ± 1.1, and a multiple correlation coefficient of 0.993. In the same way, a regression line was obtained for isomer **5** with a slope of 0.075 ± 0.008, an intercept of 11.6 ± 1.1, and a multiple correlation coefficient of 0.982.

2,2,4,4-Tetradeuterio-3-methyl-3-phenylthietane 1,1-Dioxide (18-*d*). Sulfone **18** (12 g, 0.06 mol) and a solution prepared from sodium (0.23 g, 0.01 g-atom) in deuterium oxide (5 mL, 0.28 mol) were mixed and heated with stirring on a steam bath for 6 h. The mixture was concentrated in vacuo, a fresh portion of deuterium oxide (5 mL) was added, and the mixture was heated as before. This exchange process was repeated six times. Finally, the residue was extracted with carbon tetrachloride to yield, after recrystallization from benzene–cyclohexane, **18**-*d* (8.0 g).

A sublimed portion (65 °C, 0.1 mm) gave no depression in melting point with **18**. NMR ($CDCl_3$) δ 1.78 (s, 3 H, CH_3) and 7.29 (m 5 H, C_6H_5). Mass spectrometry indicated **18**-*d* to be 94.7% d_4 and 5.3% d_3.

2,2,3,4-Tetradeuterio-3-methyl-3-phenylthietane (1-*d*) was prepared by the reduction of **18**-*d* using lithium aluminum hydride as **18** was reduced to **1**: NMR ($CDCl_3$) δ 1.72 (s, 3 H, CH_3), 7.18 (m, 5 H, C_6H_5). Mass spectrometry indicated **1**-*d* to be 94.37% d_4 and 5.7% d_3.

2,2,4,4-Tetradeuterio-3-methyl-3-phenylthietane 1-oxides 2-*d* and 3-*d* were prepared by oxidation of **1**-*d* using hydrogen peroxide as **1** was oxidized to a mixture of **2** and **3**. A mixture melting point of **2** with **2**-*d* and of **3** with **3**-*d* gave no depression. **2**-*d*: NMR ($CDCl_3$) δ 1.64 (s, 3 H, CH_3), 7.30 (m, 5 H, C_6H_5). **3**-*d*: NMR ($CDCl_3$) δ 1.43 (s, 3 H, CH_3), 7.19 (m, 5H, C_6H_5). Sulfoxide **2**-*d* contained at most 4.4% of **3**-*d*; **3**-*d* contained at most 2.5% of **2**-*d*.

3-Methyl-3-phenylthietane-*N*-(*p*-toluenesulfonyl)sulfilimines 6 and 7. Thietane **1** (8.20 g, 0.0499 mol) was added in one portion to an anhydrous solution of Chloramine-T in DMF (140 mL; 0.0553 mol of Cl[53]) kept at 5 °C in an ice bath. After 30 min, the mixture was poured into water (700 mL). The solids were collected and washed with water, 10% sodium hydroxide, and water again to give **6** and **7** (15.85 g, 95% yield). NMR analysis by integration of the 3-methyl signals ($CDCl_3$–C_6H_5) gave 54.5 ± 2.5% of **6** and 45.5 ± 2.5% of **7**. Isomer **6** crystallized from a benzene–ether solution of the mixture: IR (KBr) 970 cm^{-1} (S=N); NMR ($CDCl_3$) δ 7.34–7.94 (m, 9 H, ArH), 4.20 (broad, 2 H, J = 11.0 Hz, SCH_aH_e), 3.81 (d, J = 11.0 Hz, SCH_aH_e), 2.48 (s, 3 H, $ArCH_3$), 1.72 (s, 3 H, CH_3). Irradiation at δ 1.72 caused the δ 4.20 broad doublet to become sharp.

Isomer **7** was obtained from the residue by recrystallization from 2-propanol: IR (KBr) 990 cm^{-1} (S=N); NMR ($CDCl_3$) δ 7.33–7.89 (m, 9 H, ArH), 4.14 (s, 4 H, CH_2S), 2.38 (s, 3 H, $ArCH_3$), 1.67 (s, 3 H, CH_3). In benzene the δ 4.14 singlet separated into a doublet of doublets with additional fine structure.

An anhydrous DMF solution of Chloramine T was prepared by distilling a mixture of Chloramine-T trihydrate (100 g, 0.355 mol), DMF (500 mL), and chlorobenzene (150 mL) at 12 mm. The bright green-yellow solution which remained after 350 mL of distillate (bp 45–64 °C) had been collected lost its titer slowly, so it was used within several days of preparation.[53] *The solution was considered potentially explosive and was treated as such.*

Control Reactions for 6/7 Product Ratio. Thietane **1** (0.669 g, 4.07 mmol) in the presence of sulfilimine **6** (0.924 g, 2.77 mmol) was converted to a mixture of **6** and **7** (2.215 g, 97% yield) by reaction with anhydrous Chloramine-T–DMF (14.5 mL, 4.73 mmol) as described above. NMR analysis gave 71.4 ± 1% of **6** and 28.6 ± 1% of **7**, compared to the values of 74% of **6** and 26% of **7** calculated on the basis of a 55:45 **6/7** product ratio.

Similar treatment of **1** (0.686 g, 4.18 mmol) and **7** (0.920 g, 2.76 mmol) with Chloramine-T–DMF (4.73 mmol) gave a mixture of **6** and **7** (2.220 g, 96% yield) consisting of 32.7 ± 1% of **6** and 67.3 ± 1% of **7**; the calculated values were 32% of **6** and 68% of **7**.

Sulfilimines **6** and **7** treated separately with an equimolar amount of anhydrous Chloramine-T–DMF were recovered without change.

3-(*p*-Bromophenyl)-3-methylthietane-*N*-(*p*-toluenesulfonyl)sulfilimines 23 and 24 were prepared from thietane **11** in the manner described for **6** and **7** and were isolated by chromatography (SiO_2; $CHCl_3$–Et_2O). Sulfilimine **23** was recrystallized from benzene: IR (mull) 971 cm^{-1} (S=N); NMR ($CDCl_3$) δ 7.11–7.92 (m, 8 H, ArH), 4.33 (broad with fine structure, 2 H, J = 11.0 Hz, SCH_aH_e), 3.93 (sh

d with fine structure, 2 H, J = 11.0 Hz, SCH_aH_e), 2.40 (s, 3 H, $C_6H_4CH_3$), 1.62 (broad s, 3 H, 3-CH_3); NMR [2:1 (v/v) C_6H_6–$CDCl_3$] δ 4.09 (broad d, 1 H, J = 11.0 Hz, SCH_aH_e), 3.17 (d, J = 11.0 Hz, 1 H, SCH_aH_e), 2.12 (s, 3 H, $C_6H_4CH_3$), 1.03 (broad s, 3 H, 3-CH_3). Irradiation at δ 1.62 caused the broad doublet at δ 4.33 to become sharp.

The more highly retained isomer, **24**, was recrystallized from 2-propanol–water: Ir (mull) 985 cm^{-1} (S=N); NMR ($CDCl_3$) δ 7.24–7.93 (m, 8 H, ArH), 4.19 (s, 4 H, CH_2S), 2.40 (s, 3 H, $C_6H_4CH_3$), 1.68 (s, 3 H, 3-CH_3); NMR [2:1 (v/v) C_6H_6–$CDCl_3$] δ 3.90 (d, J = 11.0 Hz, SCH_aH_e) 3.48 (d, J = 11.0 Hz, SCH_aH_e), 2.12 (s, 3 H, $C_6H_4CH_3$), 1.21 (s, 3 H, 3-CH_3).

3-Isopropyl-3-phenylthietane-*N*-(*p*-toluenesulfonyl)sulfilimines 25 and 26 and 3-methyl-3-nitrothietane-*N*-(*p*-toluenesulfonyl)sulfilimines 27 and 28 were prepared as descripted above using anhydrous Chloramine-T. NMR analysis of the **27–28** mixture by integration of the 3-methyl protons at δ 1.99 (width at half-height, 0.8 Hz) assigned to **28** and at δ 1.82 (width at half-height, 1.6 Hz) assigned to **27** gave the isomer distributions listed in Table II. Integration of the unassigned isopropyl methyl group signals at δ 0.82 and 0.68 (J = 7 Hz) gave the isomer distribution of **25** and **26**.

3-Methyl-3-phenylthietane-*N*-(*p*-toluenesulfonyl)sulfoximines 8 and 9, were prepared by oxidizing sulfilimines **6** and **7**, respectively, with sodium permanqanate in aqueous acetone. Oxidation of **6** gave **8** (81% yield from benzene), mp 165–166 °C, followed by resolidification: mp 174–175 °C; NMR ($CDCl_3$) δ 1.83 (s, 3 H, 3-CH_3), 2.40 (s, 3H, $C_6H_4CH_3$), 4.28 and 4.98 (d of d, 4 H, J = 14 Hz, CH_2S), 7.08–7.92 (m 9 H, ArH). Oxidation of **7** gave **9** (67% yield from aqueous MeOH): mp 190–191 °C; NMR ($CDCl_3$) δ 1.93 (s, 3 H, 3-CH_3), 2.43 (s, 3 H, $C_6H_4CH_3$), 4.70 (d of d, 4 H, CH_2S), 7.05–8.02 (m, 9 H, ArH).

***S*-Ethyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfilimine–Silver Nitrate Complex (22·$AgNO_3$).** This was prepared by adding silver nitrate (6.80 g, 0.0400 mol) to *S*-ethyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfilimine (6.15 g, 0.0200 mol) in benzene (30 mL)–chloroform (30 mL). The excess silver nitrate was filtered off, and the filtrate was treated with pentane to give the **22**·$AgNO_3$ complex (2.00 g, 21% yield): mp 130–131 °C; IR (mull) 906 cm^{-1} (S=N); NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.31 (s, 3 H, $C_6H_6CH_3$), 3.08 (m, 2 H, CH_2S), 6.97–7.95 (m, 9 H, ArH).

Thermal Equilibration of Sulfilimines 6 and 7. This was carried out at 165 °C in the same way as described for sulfoxides **2** and **3**.

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Registry No.—**1**, 66810-25-1; **1-*d***, 66810-22-8; **2**, 66810-23-9; **2-*d***, 66180-24-0; **3**, 66809-92-5; **3-*d***, 66841-99-4; **4**, 66809-94-7; **5**, 66809-96-9; **8**, 66809-97-9; **9**, 66809-98-1; **10**, 66810-26-2; **11**, 66810-27-3; **12**, 185-11-5; **13**, 66810-28-4; **14**, 66810-29-5; **15**, 66810-30-8; **16**, 66810-31-9; **17**, 66810-32-0; 18, 66809-99-2; **18-*d***, 66810-00-2; **22**·$AgNO_3$, 66810-58-0; 2-(*p*-bromophenyl)-2-methylpropane-1,3-diol, 66810-01-3; *p*-bromohydratropaldehyde, 40460-91-1; formalin, 50-00-0; 2-phenyl-2-isopropylpropane-1,3-diol, 66810-02-4; diethyl 2-isopropyl-2-phenylmalonate, 66810-03-5; diisopropyl 2-isopropyl-2-phenylmalonate, 66810-05-7; ethyl isopropyl 2-isopropyl-2-phenylmalonate, 66810-04-6; 3-methylcyclohexane-1,1-dimethanol, 66810-06-8; 3-methylcyclohexane-1-carboxaldehyde, 13076-16-9; 2-methyl-2-phenylpropane-1,3-diol, 24765-53-5; cyclohexande-1,1-dimethanol, 2658-60-8; 3-cyclohexene-1,1-dimethanol, 2160-94-3; 2-methyl-2-nitropropane-1,3-diol, 77-49-6; 2-methylcyclohexane-1,1-dimethanol, 66810-07-9; 4-methylcyclohexane-1,1-dimethanol, 65172-49-8; trimethyloxonium tetrafluoroborate, 420-37-1.

References and Notes

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New Rearrangement of Penicillin Sulfoxide

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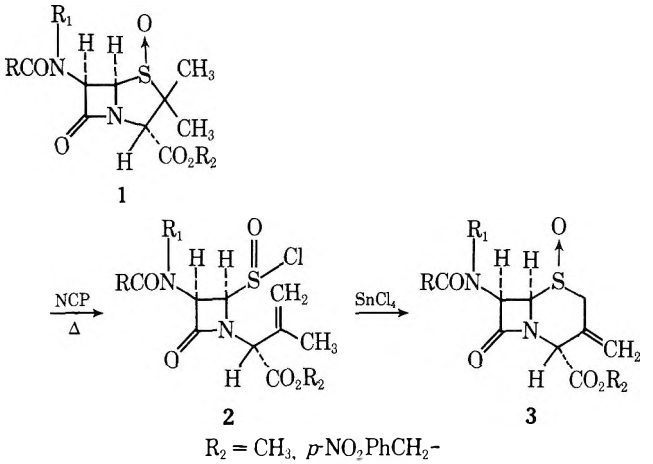
A new rearrangement resulting from cleavage of the S–C_5 bond of penicillin sulfoxide is reported. An episulfonium ion, D, is suggested as a possible intermediate. Both the six-membered ring products **4**, **5** and **6** and a five-membered ring compound, **7**, arise from the same intermediate D. Understanding the mechanism of the new rearrangement was an important step in learning how to control reaction conditions so that the desired S–C_2 cleavage reaction occurs with minimum contamination by the competing S–C_5 cleavage process.

The key intermediate in the conversion of penicillin sulfoxide **1** to *exo*-methylenecepham sulfoxide **3** is sulfinyl chloride **2**.[1] In a typical example, the synthesis of sulfinyl chloride **2** is carried out by reacting penicillin sulfoxide with *N*-chlorophthalimide (NCP) in refluxing toluene. Where R,R_1 is phthaloyl, the formation of sulfinyl chloride **2** is uneventful



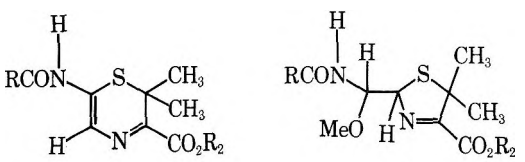
1 **2** **3**

$R_2 = CH_3$, p-NO_2PhCH_2-

and proceeds in high yield.[1] However, when R is an amide function (for example, phenoxyacetyl) and R_1 is H, a capricious side reaction often intervenes in which the reaction mixture rapidly turns dark with concomitant evolution of quantities of HCl gas. The frequency and rapidity of the side reaction increase dramatically with increasing reaction size and concentration. In the most striking examples, all of the penicillin sulfoxide is consumed in a few minutes, and two new yellow-colored products, **5** and **6**, are formed and comprise the majority of the reaction product.

Early in our investigation of this side reaction we noted that the ratio of **5** to **6** varied with time. It was subsequently demonstrated that when **5** was refluxed in toluene for a few hours, it was converted quantitatively to **6**. Furthermore, we found that trace amounts of acid greatly accelerated the conversion of penicillin sulfoxide **1** to **5** and **6** and that this side reaction could be minimized by carefully avoiding the introduction of acid and by using acid scavengers.[2]

An important clue to the mechanism of the reaction was provided by the observation that pencillin sulfoxide **1** reacts with NCP on standing in methylene chloride at room temperature (again the reaction is accelerated by the addition of acid). The product of this reaction was obtained as a yellow solid and identified as an HCl salt of compound **4**. It was crystallized from acetone as yellow needles, mp 148–150 °C.



4 **7**

R = $PhOCH_2$-; R_2 = p-NO_2PhCH_2-

Later, compound **4** was found to be a minor component of the crude reaction mixtures in which **5** and **6** were the major products, and compound **4** was subsequently isolated from these mixtures by silica gel chromatography. When the HCl salt of **4** was suspended in a toluene solution saturated with Cl_2 and heated to reflux, compounds **5** and **6** were formed, thus establishing an important link in the rearrangement.

When the HCl salt of **4** was dissolved in methanol at room temperature, the color was discharged and **7** was obtained in high yield as a white crystalline solid. Interestingly, **4** as the free imine did not react with methanol under similar conditions.

Compound **7** crystallized from methanol as white prisms, mp 119–120 °C. Elemental analysis and high-resolution mass measurements indicated a composition of $C_{23}H_{25}N_3O_7S$. Its proton NMR spectrum showed signals corresponding to an OCH_3 and an AMX system (–NH–CH(OCH_3)–CH–), in addition to the gem-dimethyl group, the phenoxyacetamido side chain, and the *p*-nitrobenzyl ester. The final structure was determined by ^{13}C NMR spectroscopy and NOE studies of the proton NMR spectrum, as well as by X-ray analysis as follows.

The unit cell of compound **7**, as determined by X-ray diffraction, contained four molecules and had the dimensions a = 23.154 (4) Å, b = 11.032 (2) Å, c = 9.659 (2) Å, and β = 98.88 (1)°, with the space group $P2_1/a$. The density calculated for $C_{23}H_{25}N_3O_7S$ was 1.328 g cm^{-3}, which was exactly the density determined by flotation. A total of 2681 reflections, of which 244 were considered unobserved, were measured on a four-angle automated diffractometer using monochromatic copper radiation. The structure was solved by phasing on the sulfur atom, located from an $E^2 - 1$ map, followed by refinement using the tangent formula. Further refinement by the the least-squares method, including anisotropic temperature factors for all heavy atoms and isotropic hydrogen atoms at assumed positions, gave a final R value of 0.068. The final heavy atom positional and thermal parameters (Table I) and the bond distances and angles (Table II) are included in the supplementary material. Figure 1 shows the extended conformation of the molecule.

The proton NMR spectrum of **4** indicated that the phenoxyacetamido side chain and the *p*-nitrobenzyl ester function were still intact; however, the proton signals corresponding to the AMX system in **7** were gone. Instead, a vinyl proton singlet at δ 7.52 and two exchangeable resonances at δ 11.0 (s, 1 H, amide NH) and ca. 11.3 (brd s of variable position) appeared. The upfield 6 H singlet at δ 1.44 indicated that the gem dimethyl groups were adjacent to a divalent sulfur such as in penicillins. In fact, examining the proton and ^{13}C spectra revealed that the partial structure shown below was

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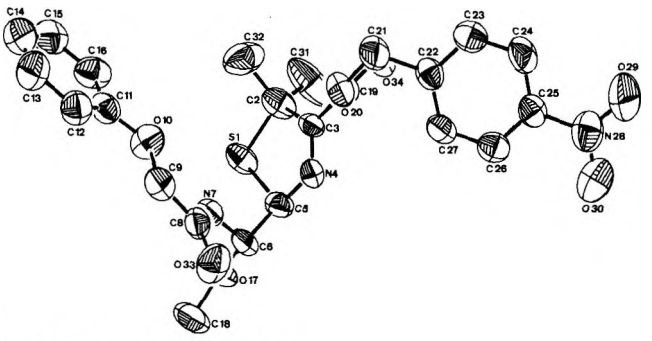
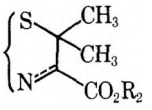
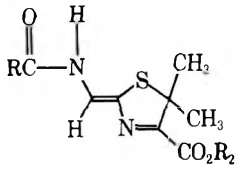


Figure 1. ORTEP drawing of **7**.

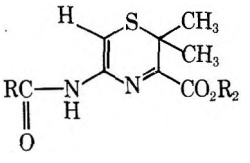
present in all other products (**4**, **5**, and **6**) in this series. In view of this evidence, only two structures (I and II) in addition to structure **4** met the structural requirements.



Of the two similar structures I and II, the latter seemed less probable since it would require N–C_5 cleavage rather than the more likely S–C_5 cleavage. We favored structure **4** of the two remaining alternatives. As described above, the proton NMR spectrum showed two discrete exchangeable proton resonances. This implies strongly that the exchange rate of the NH was quite slow. Thus, rapid chemical exchange cannot be invoked to explain an absence of vicinal coupling as in structure I. Therefore, the NH and the vinyl proton of **4** cannot be adjacent.



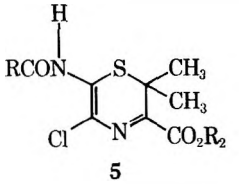
I



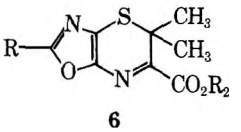
II

R = $PhOCH_2$–; R_2 = p-NO_2PhCH_2–

Having determined the structure of **4** and having established the link between **4**, **5** and **6**, their physical data were compared. Compounds **5** and **6** were readily separated and purified by silica gel column chromatography. Compound **5**, isolated as a yellow oil, had a composition of $C_{22}H_{20}N_3O_6SCl$ as determined by elemental analysis and high-resolution mass measurement. Compound **6**, crystallized from chloroform as yellow plates, mp 92–93 °C, had a composition of $C_{22}H_{19}N_3O_6S$, which amounted to the loss of HCl from **5**. The proton NMR spectrum of **5** was almost identical with that of **4** except for the vinyl proton signal which was missing from **5**. In addition, the following changes were observed in the NMR spectra of **5** and **6**. The chemical shift of the methylene protons in the side chain showed a downfield shift from δ 4.59 in **5** to δ 5.16 in **6**, and a similar change in the ^{13}C NMR spectra from δ 66.8 to 62.4 was observed. The carbonyl carbon of the side chain also shifted from δ 167.0 in **5** to δ 160.3 in **6**. These changes are consistent with a change from a phenoxyacetamido side chain in **5** to $PhOCH_2$–C(O–)=N– in **6**, and, therefore the following structures are proposed.



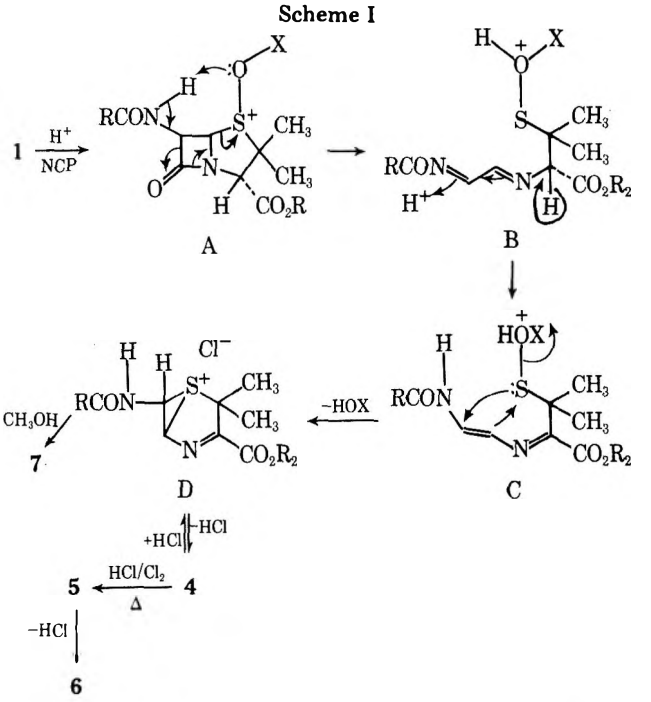
5



6

R = $PhOCH_2$–; R_2 = p-NO_2PhCH_2–

Scheme I



X = -Cl, $-COCH_2C_6H_5$, or $-SOC_6H_5R$ = $C_6H_5OCH_2$–;

R_2 = p-$NO_2C_6H_4CH_2$–

Based on the information in hand, we believe that the rearrangement occurs as outlined in Scheme I. First, NCP activated by a trace of acid reacts with penicillin sulfoxide **1** to form intermediate A, which suffers S–C_5 bond cleavage followed by loss of CO to give intermediate B. Elimination of a proton to give C is followed by ring enclosure to give episulfonium ion D. Loss of HCl from D gives compound **4**. As described earlier, the HCl salt of **4** reacts with Cl_2 (generated in situ by the reaction of HCl and NCP) to give compound **5**, which on heating loses HCl to give **6** as the final product.

The S–C_5 bond cleavage of penicillin sulfoxide followed by loss of CO and reclosure to a six-membered ring compound as outlined in Scheme I is not unprecedented. Thomas and Williams have demonstrated a similar reaction between penicillin sulfoxide and phenylacetyl chloride in the presence of aqueous acetone (in this example, ring enclosure to a six-membered ring bicyclic acetonide occurred).[3] Likewise, we found that both phenylsulfinyl chloride and phenylacetyl chloride reacted rapidly at room temperature with penicillin sulfoxide ester **1** to give the HCl salt of **4** in a manner entirely analogous to the reaction with NCP.

It is possible that the HCl salt of **4** reacts with methanol via intermediate D to give compound **7**.[4] Evidence that an episulfonium ion such as D may intervene is obtained when the reaction is carried out in deuterated methanol (MeOD). Exclusive incorporation of deuterium occurs in compound **7** at the carbon bearing the methoxy function. This result excludes a five-membered ring intermediate I as a possible precursor.

Our results indicate that the S–C_5 bond cleavage is a major (yet relatively unexplored) rearrangement pathway of penicillin sulfoxide. In addition, the unusual rearrangements which ensue offer further testimony to the wealth of chemistry which resides in the pencillin molecule.

Experimental Section

Proton NMR spectra were determined with a Varian HA-100 spectrometer and ^{13}C NMR spectra with a Jeol PFT-100 spectrometer. All solvents were spectrophotometric grade. Melting points were measured using a Thomas-Hoover capillary melting point apparatus and were uncorrected.

General Procedure for the Preparation of 4. The *p*-nitrobenzyl ester of penicillinV sulfoxide (1; R = $PhOCH_2$–, R_2 = *p*-NO_2PhCH_2–) (10 g, 20 mmol) and *N*-chlorophthalimide (4 g, 22 mmol) were mixed in 50 mL of unstabilized methylene chloride, and the suspension was stirred at room temperature until the starting materials dissolved and yellow-colored precipitate formed (about 5–6 h). The yellow precipitate was filtered, suspended in 30 mL of acetone (1 h), and filtered again to remove the soluble phthalimide. Treatment with acetone gave yellow needle-like crystals, mp 148–150 °C, in high yield. Elemental analysis showed a composition of $C_{22}H_{21}N_3O_6S$·HCl, and 7% of chlorine was free chloride. Its proton NMR spectrum showed the following signals: (Me_2SO-d_6, 100 MHz) δ 1.44 (s, 6 H, dimethyl), 4.73 (s, 2 H, $-CH_2$–OPh), 5.42 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), 6.9–8.3 (9 H, characteristic of the phenoxyacetyl and *p*-nitrobenzyl aromatic protons), 7.52 (s, 1 H, vinyl proton), and exchangeable resonances at δ 11.0 (s, 1 H, amide NH) and ca. 11.3 (brd s of variable position, 1 H, apparently HCl). Irradiation of the CH_2 group of $-CH_2$–OPh led to an NOE (7%) at one of the exchangeable proton resonances, and irradiation of the above exchangeable proton resonances led to a 13% NOE in the vinyl proton resonance. The ^{13}C NMR (Me_2SO-d_6) spectrum indicated the presence of 2 CH_3 (δ 23.4), 4 carbons of the dihydrothiazine ring (δ 38.6, 120.1, 128.8, and 143.3), and 2 ester carbons (δ 162.8 and 166.9).

General Procedure for the Preparation of 5 and 6. The *p*-nitrobenzyl ester of pencillinV sulfoxide (1; 25 g, 50 mmol) and *N*-chlorosuccinimide (10 g, 67 mmol) were heated to reflux for 20 min in 250 mL of 1,1,2-trichloroethane. At this time, the reaction mixture was very dark and no starting material remained by TLC. A large quantity of HCl gas can be seen (NH_4OH) evolving from the condenser. The reaction mixture was extracted three times with 500 mL of saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed by rotary vacuum evaporation. Thin-layer chromatography showed that the mixture was mostly compound **5**, and it was isolated by column chromatography (750 g of silica gel eluted with 40% ethyl acetate–hexane). Heating **5** in toluene for ca. 3 h gave **6** in high yield.

Alternately, instead of isolating **5**, the crude reaction mixture from above was redissolved in toluene and refluxed overnight. Purification was carried out by column chromatography as before to give compound **6** as a gum which can be crystallized by the addition of a small amount of chloroform.

Compound **5**, isolated as a yellow oil, analyzed for $C_{22}H_{20}N_3O_6SCl$, and FDMS showed a molecular ion at *m/e* 489. Its proton NMR spectrum showed the following signals: ($CDCl_3$, 60 MHz) δ 1.56 (s, 6 H, dimethyl), 4.59 (s, 2 H, $-CH_2$–OPh), 5.38 (s, 2 H, $-CH_2$–Ph*p*-NO_2), and 6.9–8.3 (9 H, characteristic of phenoxyacetyl and *p*-nitrobenzyl aromatic protons). The ^{13}C NMR spectrum (Me_2SO-d_6) indicated the presence of 2 CH_3 (δ 23.6), 4 carbons on the dihydrothiazine ring (δ 40.6, 119.5, 123.6, and 146.1), and 2 ester carbons (δ 161.9 and 167.0).

Compound **6**, crystallized from $CHCl_3$ as yellow plates, mp 92–93 °C, analyzed for $C_{22}H_{19}N_3O_6S$, and FDMS showed a molecular ion at *m/e* 453. Its proton NMR spectrum showed the following signals: ($CDCl_3$, 100 MHz) δ 1.66 (s, 6 H, dimethyl), 5.16 (s, 2 H, $-CH_2$–OPh), 5.40 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), and 6.9–8.3 (9 H, characteristic of the phenoxyacetyl and *p*-nitrobenzyl aromatic protons). The ^{13}C NMR spectrum (Me_2SO-d_6) indicated the presence of 2 CH_3 (δ 25.5), 4 carbons on the thiazine ring (δ 44.9, 127.3, 145.3, and 148.4), 1 carbon on the oxazole ring (δ 160.3), and 1 ester carbon (δ 162.3).

Conversion of Compound 4 to 7. The thiazine derivative **4** (2 g) was dissolved in methanol (10 mL), and if a small amount of phthalimide remained it was removed by filtration. Gradually the yellow color of the filtrate disappeared, and colorless crystals formed in high yield. The product was filtered off and dried to give tetrahydrothiazoline **7** as white prisms, mp 119–120 °C, microanalyzed for $C_{23}H_{25}N_3O_7S$, and FDMS showed a molecular ion at *m/e* 487 and also *m/e* 293 and 194, corresponding to the fragments cleaved between the carbon holding OCH_3 and the thiazine ring. Its proton NMR spectrum showed the following signals: (Me_2SO, 100 MHz) δ 1.64 (s, 6 H, dimethyl), 3.26 (s, 3 H, $-OCH_3$), 4.58 (s, 2 H, $-CH_2OPh$), 5.44 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), 5.41 (dd, *J* = 9.5 and 4.5 Hz, 1 H, –CH–OCH_3), 6.02 (d, *J* = 4.5 Hz, 1 H, –CH–S), 8.04 (d, *J* = 9.5 Hz, 1 H, –NH), and 6.8–8.3 (9 H, characteristic of phenoxacetyl and *p*-nitrobenzyl aromatic protons). Irradiation of the CH_2 group of the phenoxyacetamido side chain and the *p*-nitrobenzyl ester function led to sharpening of the ortho protons of the respective aromatic rings. However, irradiation of the protons of the OCH_3 group leads to no NOE anywhere in the AMX system, indicating a confirmation which maintains the OCH_3 group distant from the AMX protons. The ^{13}C NMR spectrum showed 2 CH_3 (δ 29.1 and 29.6), 1 Me_2C– (δ 64.1), 1 –C(N)H–S (δ 80.8), 1 C(OMe)H–N ((Me_2SO-d_6) δ 80.3), 1 OCH_3 (δ 161.0), and 2 ester carbons (δ 168.6 and 168.4).

Reaction of 1 with Benzenesulfinyl Chloride. To a suspension of 20 g of **1** in 300 mL of acetone was added 10 mL of benzenesulfinyl chloride. After stirring for 30 min, all of the solid material had dissolved and shortly afterwards a yellow product started to precipitate. Stirring at room temperature was continued for a total of 2 h, and 6.2 g of yellow crystalline product was filtered off. The crystals (650 mg) were recrystallized from 50 mL of boiling acetonitrile. Next morning tiny needles of the HCl salt of **4**, mp 148–150 °C, were collected. Anal. Calcd for $C_{22}H_{22}N_3O_6SCl$: C, 53.82; H, 4.31; N, 8.56; S, 6.53; Cl, 7.22. Found: C, 54.05; H, 4.56; N, 8.69; S, 6.76; Cl, 6.88.

Acknowledgment. The authors wish to thank J. L. Occolowitz for the mass spectra analysis and J. W. Paschal and T. K. Elzey for NMR measurements. We express our appreciation to Professor J. E. Baldwin for useful discussions during the course of this work.

Registry No.—**1** (R = $PhOCH_2$–; R_2 = *p*-NO_2PhCH_2–), 29707-62-8; **4**, 67194-57-4; **4** HCl, 67194-58-5; **5**, 67194-59-6; **6**, 67194-60-9; **7**, 67194-61-0.

Supplementary Material Available: Tables I and II of atomic parameters and bond distances and angles for **7** (4 pages). Ordering information is given on any current masthead page.

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(4) An alternate mechanism would involve the addition of methanol to the protonated enol ester of compound **4** followed by rearrangement to the observed five-membered ring product **7**.

Base-Catalyzed Condensations of *o*-Phthalaldehyde with Urea and Thiourea

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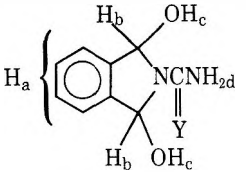
At room temperature *o*-phthalaldehyde reacts with thiourea in the presence of aqueous sodium hydroxide to form **1a** and/or **2a**. Analogous products (**1b** and **2b**) are produced in similar reactions with urea. Mechanism of formation and stereochemistry of these products are discussed. In methanolic or ethanolic solutions of the corresponding sodium alkoxides, *o*-phthalaldehyde reacts with urea or thiourea to yield monoalkoxy derivatives of **2a** and **2b** (**3a–d**); acidification of these alcoholic alkoxide reaction mixtures results in formation of dialkoxy derivatives (**4a–d**).

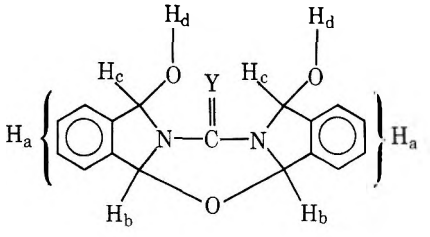
Base-catalyzed condensations of *o*-phthalaldehyde with primary amides have been shown to result in formation of *N*-acetyl-1,3-dihydroxyisoindolines or 1-hydroxy-3-amidylphthalans.[1] The determining factor in the type of product formed is the steric nature of the R group of the primary amide;[1b] products of the latter type have been isolated only when R is relatively large.

Similar reactions of *o*-phthalaldehyde with urea and thiourea have now been investigated. The relatively small size of the amino group led us to anticipate that products should be isoindoline derivatives.[2] At room temperature in dilute aqueous sodium hydroxide thiourea reacts smoothly with *o*-phthalaldehyde to yield *N*-thiocarbamyl-1,3-dihydroxyisoindoline (**1a**). When the basic filtrate from which **1a** was



1a, Y = S
b, Y = O

isolated is allowed to stand for 24 h, a second product, 2,3:5,6-dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacene-8-thione (**2a**), is isolated. The product (**2a**) may



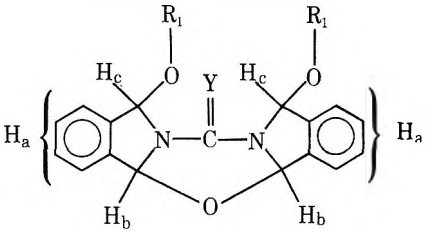
2a, Y = S
b, Y = O

also be prepared directly from *o*-phthalaldehyde (**1a**) and aqueous sodium hydroxide, and in poor yield, from **1a** alone in aqueous sodium hydroxide. *o*-Phthalaldehyde was detected in the filtrate of the last reaction. These facts indicate an equilibrium system in which the product obtained is dependent on reaction conditions (see Experimental Section).

Reaction of urea with *o*-phthalaldehyde under conditions used for the preparation of **1a** proceeds rapidly to yield only **2b**. In the presence of a large excess of urea and under the exact conditions described in the Experimental Section, pure **1b** is isolated in high yield. Again, an equilibrium system is obviously operating.

Chemically, **1a**, **2a**, and **2b** behave as expected. Attempts to oxidize them or to use acid-catalyzed hydrolysis were unsuccessful. Base-catalyzed hydrolysis yields α-hydroxy-*o*-toluic acid.[1] All attempts to chemically characterize **1b** resulted in formation of **2b**.

Similar condensations of thiourea and urea with *o*-phthalaldehyde take place in methanolic sodium methoxide and in ethanolic sodium ethoxide. Primary products were shown to be **3a–d** (R_2 = H). Acidification of filtrates from such reactions or acidification of initial reaction mixtures results in formation of **4a–d**. That formation of the second azaacetal linkage in compounds **4a–d** is due to workup of reaction mixtures (i.e.,



3a, R_1 = CH_3; Y = S
b, R_1 = CH_3; Y = O
c, R_1 = C_2H_5; Y = S
d, R_1 = C_2H_5; Y = O

4a, R_1 = R_2 = CH_3; Y = S
b, R_1 = R_2 = CH_3; Y = O
c, R_1 = R_2 = C_2H_5; Y = S
d, R_1 = R_2 = C_2H_5; Y = O

acidification) was verified by allowing compounds of structure **3** to react with acidic methanol or ethanol; products were the corresponding compounds **4**. As expected, it is possible to form both azaacetal linkages by using acid catalysis. This was demonstrated by the conversion of **2b** to **4d** using dilute acid as catalyst.

Structural assignments for all compounds are strongly supported by infrared (see Experimental Section) and nuclear magnetic resonance spectra (Table I). The NMR spectra of the urea adducts, **1b**, **2b**, and **3b**, are deceptively simple. They remain so even when run at 100 MHz. Fortunately, the thiourea analogues show much more complex spectra; it is even possible to observe coupling of H_b protons with H_c protons across the five-membered ring(s) in **2a**, **3a**, and **3c**.

The NMR spectra of **2a**, **3a**, **3c**, and **4a–d** also provide important information about the stereochemistry of these compounds, since they indicate that the OH and/or OR groups have identical orientations with respect to the C=S or C=O groups. It is unlikely that **2b** or **3b** would differ in this respect. Further, the IR spectrum of **2b** shows very broad OH absorption, indicating strong hydrogen bonding with the >C=O. Models show that such a situation obtains only when the OH groups are cis to each other and in nearly the same plane as the >C=O.

If in the reasonable diadduct intermediate, **5**, the starred OH groups were in the transoid conformation, models indicate that formation of the tetrahydro-4*H*-1,3,5-oxadiazin-4-one (or thione) ring would require introduction of much strain in that ring system as well as much distortion of the five-mem-

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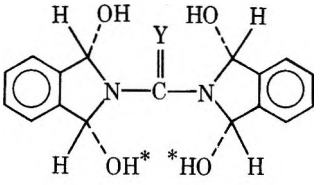
Table I. NMR Spectra of Reaction Products of o-Phthalaldehyde with Urea and Thiourea[a]

compd	registry no.	H_a	H_b	H_c	H_d	other
1a	67209-35-2	7.47 (s, 4)	6.38 (d, 2, 7.5)	5.83 (d, 2, 7.5)[b]	7.25 (s, 2)[b,c]	
1b	67209-36-3	7.42 (s, 4)	6.10 (s, 6)[b,d]	see H_b	see H_b	
2a	67209-37-4	7.52 (s, 8)	6.67 (d, 2, 2)	7.17 (2d's, 2, 2.2, 7.5)	6.62 (d, 2, 7.5)[e]	
2b	67209-38-5	7.48 (s, 8)	6.50 (s, 6)[d,e]	see H_b	see H_b	see H_b
3a	67209-39-6	7.58 (s, 8)	6.78 (d, 2, 1.5)	7.29 (d, 1, 1.5),[f] 7.25 (2d's, 1, 1.5, 7.5)[f]		–OH 6.73 (d, 1, 7.5),[g] OCH_3 3.44 (s, 3)
3b	67209-40-9	7.52 (s, 8)	6.55 (m, 5)[h]	see H_b		OCH_3 3.38 (s, 3)
3c	67209-41-0	7.52 (s, 8)	6.68 (m, 3)[i]	7.10 (m, 1, 1.5)[j] 7.25 (d, 1, 1.5)[j]		OCH_2 3.87 (q, 7), CH_3 1.19 (t, 3, 7)
3d	67209-42-1	7.50 (s, 8)	6.52 (s, 5)[h]	see H_b		OCH_2 3.78 (q, 2, 7), CH_3 1.17 (t, 3, 7)
4a	67209-43-2	7.42 (s, 8)	6.36 (d, 2, 1.5)	7.18 (d, 2, 1.5)		CH_3 3.65 (s, 6)
4b	67209-44-3	7.55 (s, 8)	6.49 (d, 2, 2)[k]	6.63 (d, 2, 2)[k]		CH_3 3.38 (s, 6)
4c	67209-45-4	7.41 (s, 8)	6.36 (d, 2, 1.8)	7.20 (d, 2, 1.8)		OCH_2 4.04 (q, 2, 7) CH_3 1.27 (t, 3, 7)
4d	67209-46-5	7.44 (s, 8)	6.39 (d, 2, 2)[k]	6.49 (d, 2, 2)[k]		OCH_2 3.57 (q, 4, 7) CH_3 1.08 (t, 6, 7)

[a] Data in table is given as chemical shifts in ppm (δ) downfield from Me_4Si (multiplicity, relative area, J in Hz); solvent used was Me_2SO-d_6 except for three compounds: 1a cetone; 4a and 4c, CCl_4. [b] Signals for H_c and H_d disappear when D_2O is added. [c] Very broad absorption. [d] Absorption is for H_b, H_c, and H_d. [e] Signal for H_d disappears when D_2O is added. [f] Obviously, these two hydrogen atoms are nonequivalent; the higher field signal must be assigned to CHOH (cf. coupling constants). [g] Overlap of the OH signal with the H_b signal occurs; however, the splitting pattern is clear. [h] For H_b, H_c, and OH; addition of D_2O reduces relative area to 4. [i] For H_b and OH; addition of D_2O reduces relative area to 2. [j] Although all coupling constants could not be measured, the multiplicity of the higher field signal requires that it be assigned to CHOH. [k] Assignments were made by analogy to the corresponding thiourea derivative; run at 90 °C to effect solution.

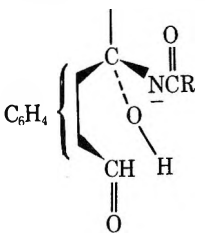
bered rings. Conversely, were these groups in the cisoid conformation, the steric situation would be very favorable for ring closure. We postulate that **5** has the structure shown and that



5

2a and **2b** have the cis-syn-cis configuration. Such a postulation requires that the monoadducts form stereoselectively and have cis OH groups.

Assuming that the mechanism of formation of the monoadducts involves attack of an amide anion on one formyl group of o-phthalaldehyde followed by proton loss and gain to yield an intermediate (**6**), it is possible to explain the ste-



6

reochemistry of the monoadducts. As the amide ion in **6** attacks the remaining formyl group, the carbonyl oxygen must begin to move out of the plane of the benzene ring as both that atom and the carbonyl carbon begin to assume sp^3 character. Hydrogen bonding with the existing OH group, possible only if both oxygen atoms are oriented on the same side of the benzene ring, could well lower the energy of the activated complex. One should expect, then, that *cis*-1,3-dihydroxyisoindolines should be predominant products.[3]

The formation of **2a** and **2b**, **3a** and **3b**, and **4a–d**, as well as those compounds discussed in ref 1, must involve base-catalyzed azahemiacetal and/or azaacetal formation. While apparently rare, such reactions have previously been observed in methylol urea systems.[4]

Experimental Section[5]

Materials. Amides and o-phthalaldehyde were purchased from Aldrich Chemical Co., Milwaukee, Wisc., and purified by standard methods.

***N*-Thiocarbamyl-1,3-dihydroxyisoindoline (1a).** o-Phthalaldehyde (3.00 g, 0.0224 mol) and thiourea (1.80 g, 0.0224 mol) suspended in 300 mL of distilled water were treated with 5 mL of 5% aqueous NaOH added dropwise with stirring over a period of 10 min. After 4 h the product was suction filtered and recrystallized from an acetone–hexane mixture to yield 3.45 g (73%) of **1a**: mp 171–172 °C dec; IR 3300 (OH), 3200, 3400 (NH_2), 744 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.47; H, 4.93; N, 13.46; S, 15.19.

2,3:5,6-Dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacene-8-thione (2a). Method A. After 24 h of standing at room temperature, the filtrate from preparation of **1a** was filtered and recrystallized from acetonitrile to yield 0.25 g (7%) of **2a**: mp 201.0–201.5 °C dec; IR 3500 (OH), 748 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58; S, 9.82. Found: C, 62.62; H, 4.31; N, 8.65; S, 9.89.

Method B. A mixture of pure **1a** (0.5 g, 2.38 mmol), 1 mL of 2.5% aqueous NaOH, and 50 mL of distilled water was stirred for 7 days. Suction filtration yielded 0.116 g of a mixture of **1a** and **2a**. Dissolution in hot methanol, addition of water until cloudiness developed, and suction filtration yielded 0.034 g of essentially pure **2a**, mp 200.5 °C dec. Removal of solvent by rotary evaporation gave 0.112 g of essentially pure **1a**, mp 170–172 °C dec. The filtrate showed a positive test for o-phthalaldehyde.[6]

Method C. o-Phthalaldehyde (1.00 g, 0.0075 mol) was added to 75 mL of distilled water. After solution was affected by heating, a solution of thiourea (0.57 g, 0.0075 mol) in 60 mL of distilled water was added; this was followed by addition of 12 mL of 2.5% aqueous NaOH. After stirring for 2 days at room temperature and suction filtration, the product was recrystallized from acetonitrile to yield 1.27 g (52%) of **2a**.

***N*-Carbamyl-1,3-dihydroxyisoindoline (1b).** A large excess of urea (2.69 g, 0.0448 mol) was added to 100 mL of distilled water. Stirring was begun, and 5 mL of 2.5% aqueous NaOH was added. o-Phthalaldehyde (3.00 g, 0.0224 mol) was added immediately and washed into the mixture with 50 mL more of distilled water.[7] After

5 days the product was suction filtered and recrystallized from acetonitrile to yield 3.51 g (81%) of **1b**: mp 172–173 °C dec; IR 3300 (OH), 3200, 3400 (NH_2), 1640 (amide I C=O), 744 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.15; N, 14.43. Found: C, 55.85; H, 5.18; N, 14.30.

2,3:5,6-Dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-s-indacen-8-one (2b). A stirred mixture of *o*-phthalaldehyde (3.15 g, 0.0235 mol), urea (0.67 g, 0.112 mol), and 100 mL of distilled water was treated with 5 mL of 2.5% aqueous NaOH; stirring was continued for 6 days. Recrystallization of the suction-filtered crystals from acetonitrile yielded 2.75 g (80%) of **2b**: mp 218–219 °C dec; IR 3333 (OH, v br), 1653 (amide I C=O), 720–780 (CH out-of-plane deformation)[8] cm^{-1}; mass spectrum *m/e* 310 (M), 309 (M − 1), 308 (M − 2), 307 (M − 3), aromatic cluster *m/e* 77, 78, 79.

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.81; H, 4.52; N, 9.03. Found: C, 65.92; H, 4.55; N, 8.97.

Monomethoxy, Monoethoxy, Dimethoxy, and Diethoxy Derivatives of 2a and 2b: 3a–d and 4a–d. All compounds were prepared by a modification of the method described in ref 1a. Urea or thiourea (0.015 mol), added to a solution of the sodium alkoxide (0.030 g at Na in 50 mL of the alcohol), was added dropwise over a period of 15 min to a rapidly stirred solution of *o*-phthalaldehyde (4.02 g, 0.030 mol) in 200 mL of the alcohol. In all cases, 24 h of stirring and standing for 2 weeks, a small amount of precipitate was evident. This was removed by suction filtration, and the filtrate was divided into two equal portions. One portion was immediately concentrated on a rotary evaporator. Resulting crystals were suction filtered, combined with the original precipitate, and recrystallized from acetonitrile. They were shown to be the monoalkoxy derivatives, **3a–d.** The second portion of filtrate was acidified with 6 N HCl until pHydrion paper showed a pH of ~1 when precipitation began. Dropwise addition of 6 N HCl was continued until reaction mixtures contained voluminous precipitates. Crystals were suction filtered, recrystallized from acetonitrile, and shown to be the dialkoxy derivatives **4a–d.** Further precipitation occurred for ~1 week. All derivatives gave positive Zeisel tests.

Yields (%) and melting points (dec): **3a,** 28, 180–182 °C; **3b,** 33, 205–206 °C; **3c,** 58, 192–193 °C; **3d,** 21, 218–219 °C; **4a,** 64, 173–174 °C; **4b,** 52, 227–228 °C; **4c,** 12, 179–180 °C; **4d,** 31, 229–230 °C. IR (cm^{-1}): OH 3400 (**3a**), 3440 3380 (**3c**), 3430 (**3d**); amide I C=O 1655 (**3b**), 1655 (**3d**), 1650 (**4b**), 1666 (**4d**); CH out-of-plane deformation 755 (**3a**), 754 (**3c**), 747 (**4a**), 750 (**4c**), see ref 8 for **3b, 3d, 4b,** and **4d.**

Anal. Calcd for $C_{18}H_{16}N_2O_3S$ (**3a**): C, 63.51; H, 4.74; N, 8.23, S, 9.42. Found: C, 63.40; H, 4.71; N, 8.24; S, 9.34. Calcd for $C_{18}H_{16}N_2O_4$ (**3b**): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.77; H, 5.06; N, 8.67. Calcd for $C_{19}H_{18}N_2O_3S$ (**3c**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.44; H, 5.10; N, 7.82; S, 8.97. Calcd for $C_{19}H_{18}N_2O_4$ (**3d**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.17; H, 5.36; N, 8.23. Calcd for $C_{19}H_{18}N_2O_3S$ (**4a**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.27; H, 5.00; N, 7.97; S, 9.12. Calcd for $C_{19}H_{18}N_2O_4$ (**4b**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.32; H, 5.30; N, 8.24. Calcd for $C_{21}H_{22}N_2O_3S$ (**4c**): C, 65.95; H, 5.80; N, 7.32; S, 8.32. Found: C, 65.77; H, 5.81; N, 7.29; S, 8.30. Calcd for $C_{21}H_{22}N_2O_4$ (**4d**): C, 68.86; H, 6,01; N, 7.65. Found: C, 68.55; H. 6.25; N, 7.56.

Conversion of Compounds of Structure 3 to Compounds of Structure 4. These conversions were accomplished as described for formation of compounds of structure 4 above. Yields varied from 51 to 85%.

Conversion of 2b to 4d. After stirring for 10 days, a mixture of 300 mL of 95% ethyl alcohol, 3 mL of 6 N HCl, and 0.62 g (0.002 mol) of **2b** remained heterogeneous. Heating to 70 °C resulted in homogeneity. Cooling, suction filtration, and washing with acetone and 95% ethyl alcohol yielded product (0.70 g, 96%) shown to be identical with **4d** by undepressed mixture melting point (229–230 °C) and identical IR spectrum.

Registry No.—*o*-Phthalaldehyde, 643-79-8; thiourea, 62-56-6; urea, 57-13-6.

References and Notes

(1) (a) R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, **30,** 2251 (1965); (b) R. D. Reynolds, D. F. Guanci, D. L. Arendsen, and R. F. Wickman, *ibid.*, **35,** 3940 (1970).
(2) It has been shown (ref 1b) that *N*-methylurea reacts with *o*-phthalaldehyde to form a monoadduct of the isoindoline type. Secondary amides (acetanilide, *N*-methylacetamide, *N*-methylformamide) did not react.
(3) It should further be noted that trans OH groups in the monoadducts would result in chirality. Many attempts to resolve these compounds failed.
(4) F. D. Chattaway and E. J. F. James, *J. Chem. Soc.*, 109 (1934); *Proc. R. Soc. London, Ser. A,* **137,** 481 (1932); *ibid.*, **134,** 372 (1931).
(5) Melting points were taken on a Büchi melting point apparatus previously calibrated against standard substances; IR spectra were determined on a Beckman IR 8 spectrophotometer in KBr pellets. A Varian A60 spectrometer was used for 60-MHz NMR spectra; 100-MHz spectra were run on a Varian HA-100 spectrometer. Mass spectra were determined on a Perkin-Elmer-Hitachi instrument, Model RUM-GE, at 60 °C. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or determined on a Perkin-Elmer 240 C, H, N analyzer. All stirring was magnetic, and all products isolated were white crystals.
(6) J. D. Bill and D. S. Tarbell *Org. Synth.*, **34,** 82 (1954).
(7) Many variations of this procedure were attempted. All resulted in mixtures of **1b** and **2b.** Recrystallization of **1b** must be carried out very carefully; otherwise, contamination by **2b** occurs.
(8) Six strong peaks occur in this spectral range. This pattern is typical of all compounds isolated as products from 2 mol of *o*-phthalaldehyde/mol of urea.

Catalytic Hydrogenation of Some Acylguanidines

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The behavior of several acylguanidines toward low-pressure hydrogenation over PtO_2 catalyst was investigated. Creatinine (**3**) and alacreatinine (**7a**) gave cleanly the corresponding cyclic guanidines, iminoimidazolidines **4** and **8a**. β-Alacreatinine (**9**) also could be hydrogenated in aqueous acid to iminohexahydropyrimidine **10,** but the same reaction in water gave a mixture of products. Only guanidine itself could be isolated from the hydrogenation of acetylguanidine, while the simple amide analogue pyrrolidinone was not reduced under these conditions and gave γ-aminobutyric acid under forcing conditions. The glycocyamides alacreatinine (**7a**) and phenylalacreatinine (**7b**) were prepared by acid-catalyzed cyclization of the corresponding optically active α-guanidino acids. In both cases, the resulting glycocyamidines were racemic. When the hydrogenation of creatinine was carried out in D_2O, the product 2-imino-1-methylimidazolidine (**23**) contained two deuterium atoms at C-4 and two at C-5, thus suggesting that hydrogenation would also lead to racemization of an α-chiral center.

If the preparation of alkylguanidines could be effected by reduction of the corresponding acylguanidines, the process would be of considerable utility since a variety of acylguanidines is readily available.[1,2] We have recently[3] developed a procedure using lithium aluminum hydride which accomplishes this conversion. In pursuit of perhaps an alternative and more convenient process, we have investigated the catalytic hydrogenation of acylguanidines. Such reductions of acylguanidines have not been reported. Although amides can be so reduced, the conditions necessary invariably involve high

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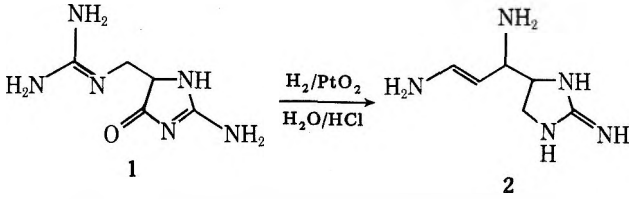


1 2

temperatures (>200 °C) and pressure (200–300 Torr).[4]

Our interest in the catalytic hydrogenation of acylguanidines was stimulated by the high yield conversion of the guanidinoglycocyamidine **1** to the cyclic guanidine **2**.[5] Was this a special case, influenced by the exo guanidine group proximal to the carbonyl, or did it reflect a general reaction? To answer this question, we examined a series of acylguanidines under hydrogenation conditions similar to those used in the preparation of **2** from **1**. We now report our catalytic reduction results.

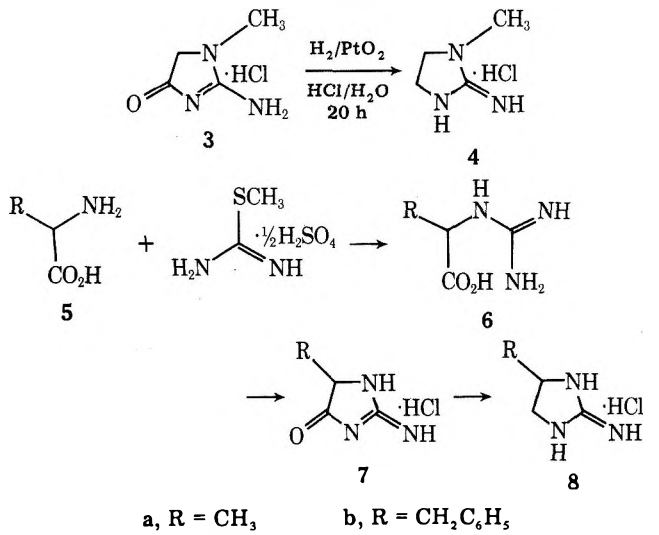
Because of its availability and similarity to the initial substrate **1**, creatinine hydrochloride (**3**) was chosen as the model compound to use in developing a set of standard hydrogenation conditions which were 0.05 M acylguanidine with 50 mol % of PtO_2 catalyst in a Parr shaker at a hydrogen pressure of 15–35 psi gauge. The reductions were monitored by withdrawing an aliquot for either NMR or UV analysis.

To our surprise, the ^1H NMR spectrum of the creatinine reaction mixture showed all the starting material to be consumed in less than 20 h of shaking at room temperature in 1.0 N HCl. ^{13}C and ^1H NMR analysis of the crude product obtained after filtration and evaporation indicated that the reduction gave cleanly the corresponding cyclic guanidine **4** in greater than 90% yield. Hydrogenations in either 0.1 N HCl or water did not make a significant difference in the rate of hydrogenation, yield, or purity of the cyclic guanidine product.

Alacreatinine hydrochloride (**7a**), a compound more directly analogous to **1**, was tried next. In contrast to creatinine, the rate of hydrogenation of alacreatinine under the above standard conditions was very slow (8 days). Cyclic guanidine **8a** was obtained, however, in good yield (Scheme I). The addition of varying amounts of acid to the solvent or the application of heat did not make consistent differences in the rate or yield. We attribute the lesser activity of alacreatnine (**7a**) to steric hindrance of its carbonyl group caused by the adjacent methyl. This added steric bulk might be a causative factor in the relatively slower hydrogenation of **7a**, although we did not anticipate a rate difference of such magnitude.

In order to explore the question of generality, two further acylguanidines were synthesized and subjected to the standard hydrogenation conditions. β-Alacreatinine hydrochloride (**9**)[2,6] was chosen as representative of the six-membered cyclic guanidine system, and acetylguanidine hydrochloride (**18**)[1] represented the open-chained series.

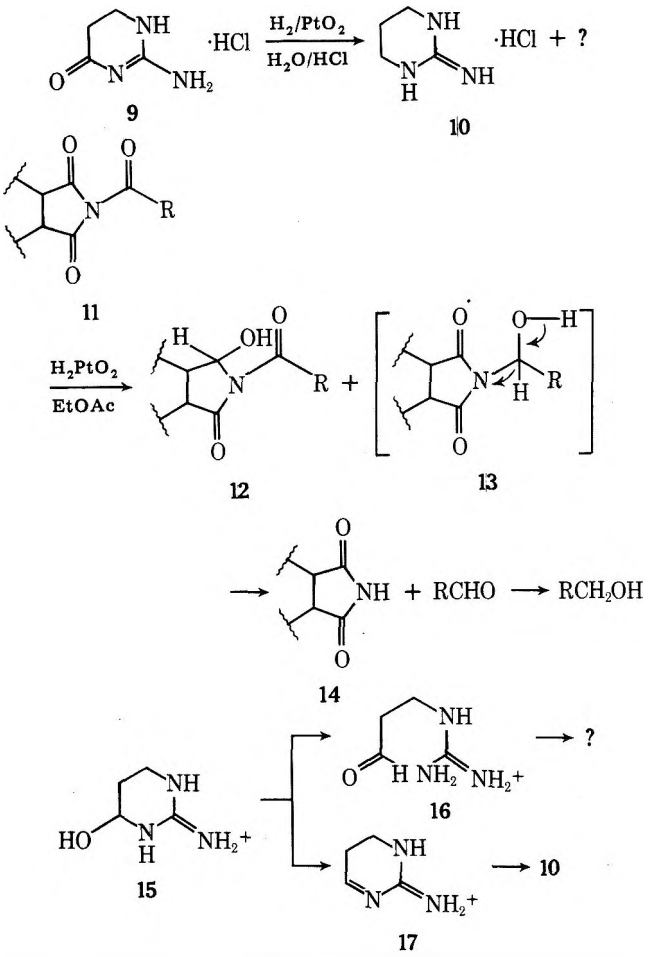
Scheme I



3 4 5 6 7 8

a, R = CH_3 b, R = $CH_2C_6H_5$

Scheme II

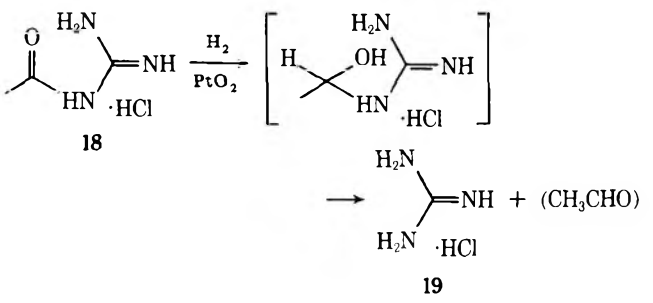


9 10 11 12 13 14 15 16 17

β-Alacreatine (**9**) was hydrogenated readily in water but gave, unexpectedly, a mixture of compounds as ascertained by NMR. Ion-exchange chromatography was utilized to separate the components, and with the strongly acid AG-50 resin and HCl as the eluent it was possible to recover the desired pure cyclic guanidine **10**. However, no other single component could be isolated, and TLC using a Weber visualizing spray[7] suggested that the product distribution was quite complex.

Although no literature precedent is available regarding the hydrogenation of acylguanidines, there is one report[8] that deals with the hydrogenation of the remotely related *N*-acylimide system. Hydrogenation of several different *N*-acylimides **11** over PtO_2 in ethyl acetate usually led to mixtures of the intact reduced hydroxylactam **12** and the parent imide **14**. Reduction presumably occurred by the same mechanism to carbinolimines **12** and **13**. In the latter case the intermediate exo carbinolimine **13** apparently fragmented in the manner indicated to give back the parent imide **14** and an aldehyde which was further reduced to an alcohol.

In the β-alacreatinine system, we thought that if the undesired side products were due to a similar fragmentation occurring from **15** to **16** in a mildly acidic milieu (the hydrochloride in water), increasing the acidity might protonate the hydroxyl group and promote the elimination of water to intermediate **17** instead of ring opening to the aldehydo guanidine **16** which then goes on to other products. It was found that addition of HCl to the reaction mixture did permit the clean hydrogenation of **9** to **10**. In 1 N HCl the hydrogenation was mostly over in 1 day and totally completed in 2 days, giving pure product in high yield as shown in Scheme II.



18 19

Acetylguanidine hydrochloride (18) failed to give any trace of the desired ethylguanidine under any of a variety of conditions, and only guanidine hydrochloride itself (19) could be isolated. The hydrogenation was carried out in both water and acid (0.1 and 1.0 N HCl). In water all starting material was consumed in less than 2 days at room temperature, and a quantitative yield of guanidine hydrochloride was isolated. A control experiment showed that 18 was stable in water for that period of time. Thus hydrogenation under these conditions probably proceeded to the intermediate carbinolguanidine stage. Fragmentation then gave guanidine hydrochloride (19) and acetaldehyde which was further reduced.

No reaction could be detected in any of the acid hydrogenations of acetylguanidine at room temperature for up to 40 h, but heating the reaction in 1 N HCl at 60 °C gave guanidine. This latter reaction was probably due in part, if not wholly, to hydrolysis since control studies indicated that 18 was hydrolyzed in 1 N HCl/60 °C at about the same rate as guanidine appeared in the hydrogenation reaction. The HCl salt was also hydrogenated in anhydrous glacial acetic acid that was 1 N in HCl, but no reaction occurred, even upon heating, as was also observed in the absence of added HCl. Attempted hydrogenation of acetylguanidine free base in water failed also. No reaction occurred at room temperature and only unidentified products were obtained upon heating.

In order to test the uniqueness of the acylguanidine hydrogenation and to conclusively rule out the possibility that a lactam might similarly be reduced under our conditions, we subjected 2-pyrrolidinone (**20**) to hydrogenation in 1 N HCl under the standard conditions. As expected, no reaction was observed at room temperature, and heating at 60 °C gave only the ring-opened γ-aminobutyric acid (**21**).

We can therefore summarize the relevant features of the above acylguanidine hydrogenation reactions. Five- and six-membered cyclic acylguanidines comprise a class of amides that are unique in that low-pressure catalytic hydrogenation reduces their carbonyl group to the level of methylene. The simple amide analogue pyrrolidinone failed to be hydrogenated under these conditions. The six-membered β-alacreatinine gave clean reduction only if acid was added, perhaps due to the fact that in water a competing fragmentation of an intermediate carbinolguanidine is operative. The simple open-chain acetylguanidine gave guanidine, probably through a carbinolguanidine intermediate, or no reaction. Also under forcing conditions in aqueous acid, guanidine was formed, but in the latter instance it is uncertain whether any reduction–fragmentation was involved or if only hydrolysis was responsible.

It is interesting to speculate why certain acylguanidines can be so easily hydrogenated while amides can not. Also, some cyclic carboxylic acid anhydrides can be hydrogenated over PtO_2 at room temperature and atmospheric pressure to the corresponding hemiacylal or lactone whereas simple esters are not reduced under these conditions.[9] The latter behavior was rationalized by proposing that the electron density at the carbonyl of anhydrides is less than that at ester carbonyls because the electron donation of the central anhydride oxygen must be shared by two carbonyls. This postulated dependence of reducibility on electron scarcity is also supported by the previously noted observation that although simple imides are not easily reduced, *N*-acylimides are so reduced.[8]

Our observations are consistent with this scheme. One would expect decreased amide resonance by donation of the nitrogen electron pair to the carbonyl in an acylguanidinium salt because this electron pair is already involved in the protonated guanidinium system. Also, the presence of this positively charged system so close to the carbonyl would tend to inductively decrease the electron density of the latter. It then becomes reasonable that the acylguanidine carbonyl should behave more like a ketone than an amide in its susceptibility to catalytic hydrogenation.

A potentially useful application of acylguanidine hydrogenation reaction would be the preparation of optically active cyclic guanidines of type **8**. Previously such compounds have been made in the *dl* form from the corresponding optically inactive diamines and an electrophilic reagent that provides the ring-forming one-carbon unit.[10] Or perhaps the optically active cyclic guanidine obtained by hydrogenation could be hydrolyzed to give an optically active diamine, which would otherwise be difficult to prepare without going through a resolution. The best starting materials for this process are, of course, the naturally occurring, optically active amino acids. The route involves reactions that have been well worked out for a number of systems, i.e., amidination of the amino acid and cyclization of the resulting α-guanidino acid to the glycocyamidine.

L-Phenylalanine (**5b**) was chosen initially as the optically active test substrate. The α-guanidino acid **6b** was prepared by standard procedures[11] and had $[\alpha]^{25}_{D}$ +42°. Cyclization to the glycocyamidine **7b** was performed in boiling, concentrated HCl, but to our surprise this latter compound was optically inactive. The simpler L-alanine system was also tried. L-Amidinoalanine (**6a**) was prepared and found to have $[\alpha]^{25}_{D}$ +10°. Cyclization with concentrated HCl gave **7a** as before but, again, the glycocyamidine was racemic.

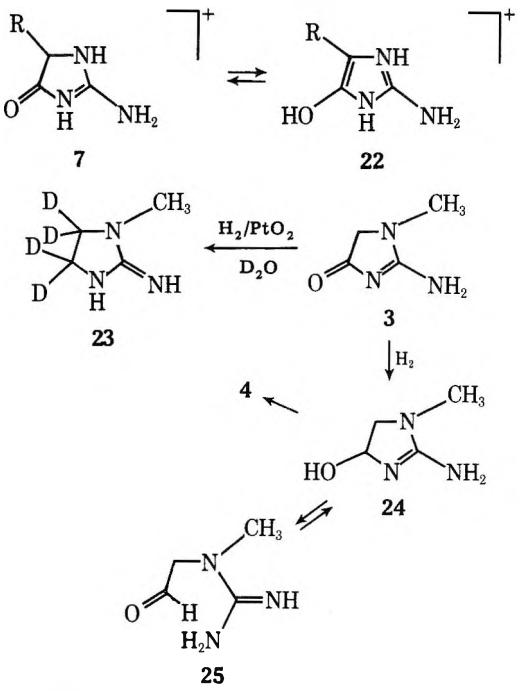
This racemization during cyclization of the α-guanidino acid to the glycocyamidine in hot, concentrated HCl was unexpected. It is known, of course, that peptides, when subjected to similar treatment, give optically active amino acids. No pertinent studies on optically active glycocyamidines have been reported and no optical activity data on these compounds have appeared. Some insight was gained in a study of exchange in D_2O. All the glycocyamidines **3, 7a, 7b** showed no deuterium incorporation at room temperature under mildly acid conditions; however, they did exchange under the more drastic conditions of the cyclization.

This exchange and racemization behavior can be explained by assuming the enolization equilibrium **7** ⇌ **22** (Scheme III). Again, the guanidinium resonance stabilization can be invoked to rationalize decreased amide-type delocalization and thus facilitate enolization.

On the assumption that milder, nonracemizing cyclization conditions could be found, we still wished to explore the hydrogenation reaction as a possible path to chiral alkylguanidines and diamines. Since the hydrogenation is conducted under conditions where the glycocyamidines do not exchange, retention of any starting chirality might be feasible. To ascertain any potential racemization, we attempted to replace the carbonyl oxygen with deuterium and conduct the reaction in D_2O. Thus by carrying out the reduction in $D_2O/Pt/H_2$ we also would take advantage of the frequently overlooked, rapid equilibration between D_2O and H_2 in the presence of platinum catalyst to form H_2O and D_2. Any racemization potential under these conditions would be detected by deuterium introduction at C-5.

To test this approach we hydrogenated creatinine (**3**) in D_2O and obtained in good yield a single crystalline product.

Scheme III



^{1}H NMR analysis of the product showed that essentially only one major absorption was present, the δ 2.9 peak assigned to the N-CH_3. There was a small absorption at δ 3.7 but this accounted for less than 10% of the total integration. Thus both of the product methylenes had fully incorporated deuterium to give the tetradeuterio derivative **23.** This assignment was confirmed by the mass spectrum which showed an $M^+ - HCl$ peak at *m/e* 103 and no appreciable $M^+ - HCl$ peak at *m/e* 99, the latter peak being exhibited by the protio compound. The $M^+ - HCl$ peaks are the most intense in both the deuterio and protio products.

It is clear from this experiment that complete exchange at the α position (C-5) took place rapidly during the hydrogenation reaction. We can postulate that this exchange proceeded through a ring-opened intermediate such as **25** which would rapidly incorporate deuterium via its enolization equilibrium and then be reduced to imidazolidine **4.** The possibility that the starting creatinine underwent exchange under the hydrogenation conditions but without hydrogenation was eliminated by a direct control experiment in which unchanged starting material was recovered. Thus this hydrogenation reaction, while a good method preparing cyclic guanidines, does not show promise as a method for synthesizing chiral compounds.

Experimental Section[12]

DL-*N*-Amidinoalanine (6a). DL-Alanine (**5a,** 4.46 g, 50 mmol) was dissolved in 1 N NaOH (50 mL, 50 mmol). To this was added *S*-methylisothiourea sulfate (6.95 g, 25 mmol), and the resulting solution was heated at 50 °C for 6 h. The water was evaporated at <70 °C, leaving a white crystalline mass which was dissolved in 30 mL of boiling water and allowed to cool to room temperature. Seeding with a pinch of the original residue gave the product as white stocky needles; recrystallization from water gave 1.5 g (23%) of **6a:** mp 218 °C dec; ^{1}H NMR δ 4.0 (q, 1 H), 1.3 (d, 3 H).

L-*N*-Amidinoalanine (6a). L-Alanine (**5a,** 4.46 g, 50 mmol) was treated with NaOH and S-methylisothiourea sulfate for 6 h as described above. After evaporation of the water the crude solid residue was recrystallized from water to give 3.37 g (52%) of **6a:** mp 215–216 °C (lit. mp[13] 247 °C); $[\alpha]^{25}_D$ +9.6° (*c* 1.04, H_2O). Anal. Calcd for $C_4H_9O_2N_3$: C, 36.6; H, 6.9; N, 32.0. Found: C, 36.3; H, 7.1; N, 31.8.

L-*N*-Amidinophenylalanine (6b). L-Phenylalanine (**5b,** 16.62 g, 100 mmol) was treated with 1 N NaOH (100 mL, 100 mmol) and *S*-methylisothiourea sulfate (13.93 g, 50 mmol) for 2 h as described above. The residue remaining after evaporation of the water was recrystallized two times from water to give 1.89 g (9%) of product as white needles: mp 241–242 °C (lit. mp[13] for DL compound, 240–242 °C); $[\alpha]^{25}_D$ +42.4 ° (*c* 1.98, 1 N NaOH). Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.3; N, 20.3. Found: C, 58.0; H, 6.4; N, 20.3.

DL-Alacreatinine Hydrochloride (7a). DL-*N*-Amidinoalanine (DL-**6a,** 1.1 g, 8.5 mmol) was refluxed for 3 h in concentrated HCl (25 mL). Evaporation of the solvent gave a white crystalline solid that was recrystallized from ethanol to give 900 mg (72%) of DL-**7a:** mp 203–204 °C (lit. mp[11] 203–204 °C); ^{1}H NMR δ 4.5 (q, 1 H), 1.5 (d, 3 H); ^{13}C NMR δ 177.3 (s), 157.1 (s), 55.5 (d), 15.4 (q).

The same result was obtained when L-*N*-amidinoalanine (L-**6a,** 2.0 g, 15.3 mmol) was refluxed with concentrated HCl (40 mL) for 3 h. The product had $[\alpha]^{25}_D$ 0° (*c* 2, H_2O).

DL-Phenylalacreatinine (2-Amino-5-phenylmethyl-4-oxo-4,5-dihydroimidazole) Hydrochloride (7b). L-*N*-Amidinophenylalanine (**6b,** 2.37 g, 11.5 mmol) was refluxed in concentrated HCl (40 mL) for 1 h. Evaporation of the solvent and recrystallization of the residue from isopropyl alcohol–ether gave 2.35 g (90%) of **7b** as flaky white crystals: mp 187–190 °C; $[\alpha]^{25}_D$ 0° (*c* 2.14, H_2O); ^{1}H NMR δ 7.6 (s, 5 H), 4.9 (m), 3.3 (d, 2 H).

Anal. Calcd for $C_{10}H_{12}N_3OCl$: C, 53.2; H, 5.4; N, 18.6. Found: C, 53.4; H, 5.4; N, 18.7.

β-Alacreatinine Hydrochloride (9). β-Alanine (8.91 g, 100 mmol) was treated with 1 N NaOH (100 mL, 100 mmol) and *S*-methylisothiourea sulfate (13.93 g, 50 mmol) for 1 h as described above. The crude *N*-amidino-β-alanine so obtained was recrystallized from water and immediately cyclized by boiling in concentrated HCl for 1 h. Evaporation and recrystallization from methanol gave 3.77 g (25% from β-alanine) of **9:** mp 265–269 °C (lit.[6] mp 268–271 °C); ^{13}C NMR δ 170.5 (s), 153.9 (s), 36.3 (t), 29.3 (t).

Acetylguanidine (18). This compound as the free base was prepared as previously reported:[1] mp 186–187 °C (lit. mp[1] 188–190 °C); ^{1}H NMR δ 2.0 (s); ^{13}C NMR 185.0 (s), 161.9 (s), 26.1 (q).

The hydrochloride salt was prepared by dissolving a portion of the free base in 1 N HCl and evaporating to dryness. The crude salt was recrystallized from ethanol–ether to give fine white needles: mp 142–144 °C; ^{13}C NMR δ 174.3 (s), 154.0 (s), 24.0 (q).

2-Imino-1-methylimidazolidine Hydrochloride (4). Creatinine hydrochloride (373 mg, 2.5 mmol), PtO_2 (88%, 342 mg, 1.25 mmol), and water (50 mL) were shaken in a Parr apparatus under 20–35 psi of hydrogen for 20 h. After filtration of the catalyst and evaporation of the solvent, 320 mg (94.5%) of **4** was obtained: ^{1}H NMR δ 3.65 (m, 4 H), 2.95 (s, 3 H); ^{13}C NMR δ 158.8 (s), 49.8 (t), 40.7 (t), 31.1 (q); MS *m/e* 99 ($M^+ - HCl$).

The picrate was formed in H_2O–ethanol from the hydrochloride: mp 195–196 °C (lit.[14] mp 194.5–195 °C).

2-Imino-4-methylimidazolidine Hydrochloride (8a). Alacreatinine hydrochloride (**7a,** 128 mg, 0.86 mmol), PtO_2 (121 mg, 0.43 mmol), and water (50 mL) were shaken with hydrogen as described above. The course of the reaction was followed by UV, monitoring the intensity of the acylguanidine absorption at 225 nm. After 8 days the 225-nm absorption had disappeared, and filtration and evaporation gave 106 mg (92%) of crystalline **8a:** ^{1}H NMR δ 4.4–3.2 (m, 3 H), 1.35 (d, 3 H); ^{13}C NMR δ 158.9 (s), 51.2 (d), 49.5 (t), 19.7 (q).

A picrate was prepared in water from the hydrochloride: mp 195–196 °C (lit.[15] mp 195–196 °C).

2-Iminohexahydropyrimidine Hydrochloride (10). A mixture of β-alacreatinine hydrochloride (**9,** 373 mg, 2.5 mmol), PtO_2 (342 mg, 1.25 mmol), and 1 N HCl (50 mL) were hydrogenated for 20 h as before. After filtration and evaporation, 305 mg (91%) of crystalline **10** were obtained: mp 150–153 °C (lit.[3] mp 153 °C); ^{1}H NMR δ 3.4 (t, 4 H), 2.1 (pentet, 2 H); ^{13}C NMR δ 153.6 (s), 38.0 (t), 19.2 (t).

A picrate was prepared from water from the hydrochloride: mp 184–187 °C (lit.[15] mp 185–186 °C).

Hydrogenation of β-Alacreatinine Hydrochloride (9) in Water. β-Alacreatinine hydrochloride (**9,** 373 mg, 2.5 mmol) and PtO_2 (342 mg, 1.25 mmol) were shaken with hydrogen as above in water (50 mL) for 19 h. Filtration and evaporation of the solvent gave a clear oil that slowly solidified. The ^{1}H NMR spectrum suggested the presence of more than one component: δ 5.5 (t, rel area 1), 3.7 (m, 8), 2.3 (m, 4.5). The crude product was chromatographed on a column of Bio-Rad AG 50-X8, −400 mesh resin (50 mL bed volume, 2 N HCl eluate). The elution was followed by TLC (silica gel, phenol saturated with water, visible with Weber spray)[7] and by this criterion **10** appeared as a deep-purple spot and could be isolated pure from the appropriate eluate fractions. The remaining fractions all contained a number of Weber-pink or red spots, and no other single compound could be isolated.

Hydrogenation of Acetylguanidine Hydrochloride (18). Acetylguanidine (**18,** 294 mg, 2.1 mmol), as the hydrochloride, and PtO_2 (342 mg) were shaken with hydrogen in water (50 mL) as before. The reaction was monitored by UV and stopped after 48 h when the

absorption at 227 nm had disappeared. Filtration and evaporation gave 203 mg (100% yield) of a white crystalline solid that proved to be identical with guanidine hydrochloride by TLC and ^{13}C NMR (δ 157.8).

When the hydrogenation was conducted in 1 N HCl no reaction was observed after shaking for 21 h at room temperature. The reaction mixture was then heated at 60 °C for 43 h at which point the UV absorption had disappeared. Filtration and evaporation of the solvent gave only guanidine hydrochloride. A duplicate reaction using 0.1 N HCl gave similar results.

Hydrogenation of Creatinine Hydrochloride (3) in D_2O. [4,5-$^2H_4$]-2-Imino-1-methyl-imidazolidine Hydrochloride (23). Creatinine hydrochloride (3, 373 mg, 2.5 mmol) was placed in an hydrogenation bottle and exchanged four times with D_2O by dissolution and evaporation. To this was then added PtO_2 (342 mg, 1.25 mmol) and D_2O (50 mL, 99.8% d), and the resultant mixture was hydrogenated as before for 26 h. After filtration and evaporation, 319 mg (89%) of a white crystalline solid was obtained: ^1H NMR δ 2.95 (s). The product was exchanged several times with water as before: MS *m/e* 104 (M^+ − HCl). A picrate was prepared in the same manner as for the nondeuterated compound 4 and showed the same melting point at 195–196 °C.

Hydrogenation of Pyrrolidinone (20). Pyrrolidinone (**20**, 213 mg, 2.5 mmol) and PtO_2 (342 mg, 1.25 mmol) were hydrogenated as before in 1 N HCl (50 mL). No reaction was apparent by ^1H NMR after 47 h at room temperature. The reaction was then heated at 60°C as described above for 88 h, after which time ^1H NMR and ^{13}C NMR (see below) showed the starting pyrrolidinone to be gone, and in its place a new product which, after filtration and evaporation, appeared as a crystalline solid: mp 133–135 °C; ^1H NMR pyrrolidinone δ 3.5 (5, t H), 2.2 (m, 4 H); hydrogenation product δ 3.0 (t, 2 H), 2.5 (t, 2 H), 2.0 (q, 2 H); ^{13}C NMR hydrogenation product δ 177.6 (s), 38.8 (t), 31.2 (t), 22.2 (t).

By comparison of melting points and NMR with that of an authentic sample, the product recovered from the hydrogenation reaction was established as γ-aminobutyric acid hydrochloride (**21**).

Registry No.—**3**, 19230-81-0; **4**, 67316-70-5; DL-**5a**, 302-72-7; L-**5a**, 56-41-7; **5b**, 63-91-2; DL-**6a**, 67337-40-0; L-**6a**, 1758-74-3; **6b**, 13551-04-7; **7a**, 67316-71-6; **7b**, 67316-72-7; **8a**, 67316-73-8; **9**, 15231-28-4; **10**, 26893-39-0; **18**, 5699-40-1; 18 HCl, 39270-72-9; **20**, 616-45-5; **23** HCl, 67316-74-9; **23** picrate, 67316-76-1; *S*-methylisothiourea sulfate, 867-44-7; β-alanine, 107-95-9.

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Synthesis of 1-Substituted Tricyclo[3.3.1.$0^{2,7}$]nonanes

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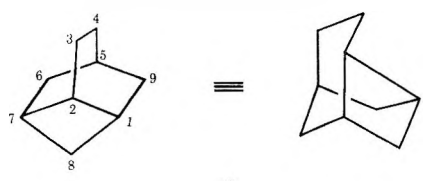
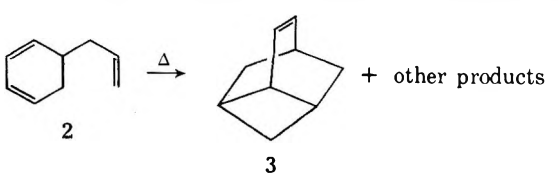
1-Acetyltricyclo[3.3.1.$0^{2,7}$]non-3-ene (**15**) has been prepared by a five-step reaction sequence from 3-*endo*-carboxybicyclo[3.3.1]non-6-ene. The skeletal framework of **15** follows from its conversion to the parent hydrocarbon, tricyclo[3.3.1.$0^{2,7}$]nonane. Alternative conditions for the epimerization of 3-*endo*-acetylbicyclo[3.3.1]non-6-ene have been determined.

Although the synthesis of tricyclo[3.3.1.$0^{2,7}$]nonane (**1**) has not been reported previously, two independent routes leading to compounds which contain this carbon skeleton are

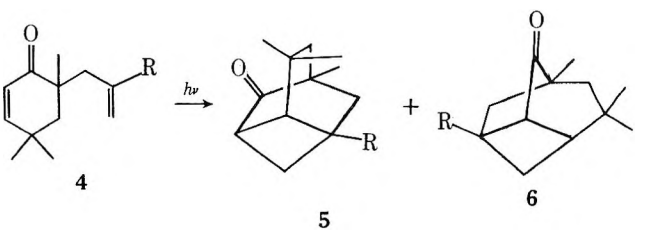


1

known. In 1967 Krantz noted that pyrolysis of 5-allylcyclohexa-1,3-diene (**2**) at 225 °C gives tricyclo[3.3.1.$0^{2,7}$]non-3-ene (**3**) as well as 1-allylcyclohexa-1,3-diene, 2-allylcyclohexa-1,3-diene, benzene, and recovered starting material.[2] Through labeling studies it was established that **3** is formed from **2** at 184 °C by a [4 + 2] cycloaddition mechanism.[3] At higher temperatures at least one other mechanistic pathway becomes competitive.[3] More recently, Frőstl and Margaretha have found that irradiation of various 6-allyl-4,4,6-trimethyl-2-cyclohexenones (**4**) gives mixtures of the isomeric tricyclononanones **5** and **6**.[4] The product ratio depends on the substituent R of the allylic side chain and is somewhat influenced by the solvent.[4] We now wish to report an alternative synthesis of the tricyclo[3.3.1.$0^{2,7}$]nonane skeleton which permits the



2 **3**



4 **5** **6**

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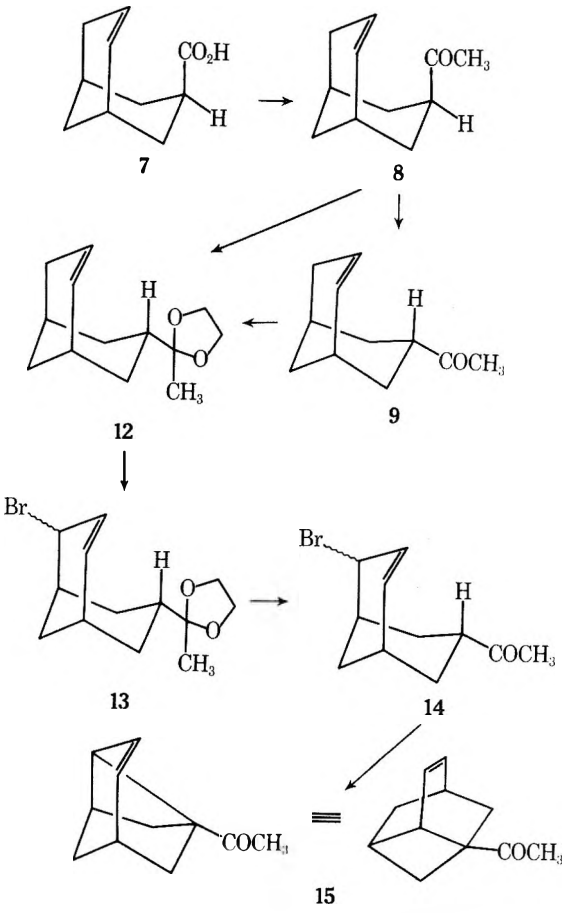
Scheme I

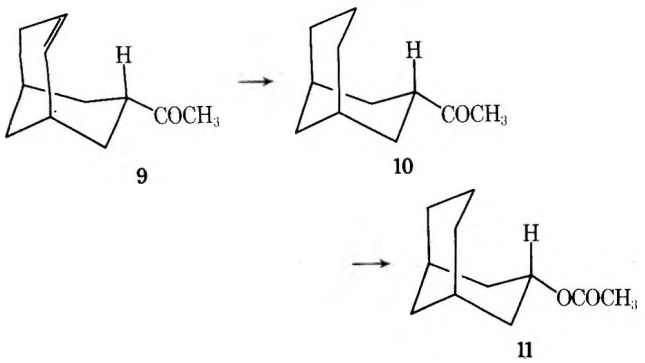


introduction of a variety of substituent groups at C-1. In the course of this study, we have also prepared the parent hydrocarbon **1**.

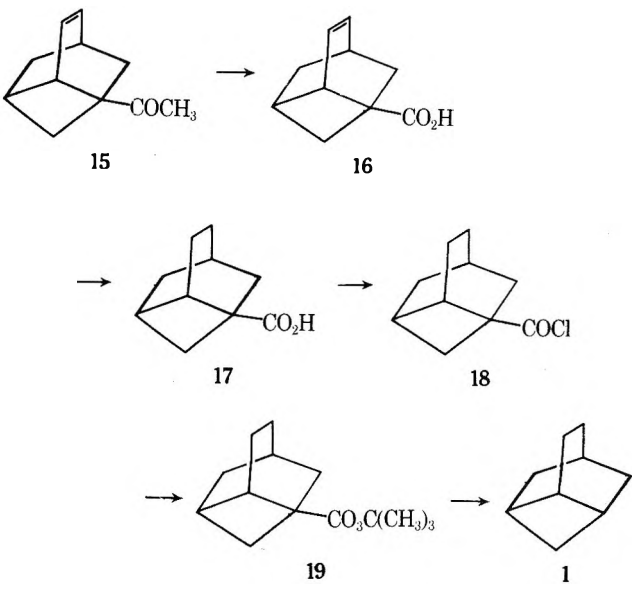
Results and Discussion

By inspection, it is apparent that **1** can be viewed as a "dehydro"bicyclo[3.3.1]nonane. Consequently, 3-*endo*-carboxybicyclo[3.3.1]non-6-ene (**7**), an acid which can readily be prepared from commercially available 2-adamantanone,[5] was selected as starting material. The sequence of reactions leading from **7** to 1-acetyltricyclo[3.3.1.0^{2,7}]non-3-ene (**15**) is summarized in Scheme I.[6]

Treatment of **7** with methyllithium provides 3-*endo*-acetylbicyclo[3.3.1]non-6-ene (**8**). Epimerization of **8** to ketone **9** can be accomplished under a variety of conditions: by refluxing **8** with a trace of *p*-toluenesulfonic acid in benzene, by treating **8** with potassium *tert*-butoxide in *tert*-butyl alcohol, or by heating **8** at 200–205 °C in a sealed ampule. As might be expected, the spectral properties of **8** and **9** are strikingly similar. However, they are readily differentiated as the olefinic protons of **9** are shifted downfield ca. 0.3 ppm relative to the olefinic protons of **8**. The skeletal framework of **9** and the



Scheme II



skeletal position and stereochemistry of the acetyl group in **9** were firmly established by its conversion to the previously reported 3-*exo*-acetoxybicyclo[3.3.1]nonane[7] (**11**). Catalytic hydrogenation of **9** gives 3-*exo*-acetylbicyclo[3.3.1]nonane[8] (**10**) and Baeyer–Villiger oxidation of **10** with *m*-chloroperbenzoic acid provides **11**.

In order to carry out bond formation between C-3 and C-8 in **9**, it was necessary to introduce an appropriate leaving group at C-8. Since attempts to affect direct allylic bromination of **9** only led to complex reaction mixtures, the ketone was first converted to the corresponding ethylene ketal **12**.[9] Reaction of **12** with *N*-bromosuccinimide under free-radical conditions provides bromo ketal **13** in quantitative yield and treatment of this ketal with dilute acid in acetone gives the desired 7-*exo*-acetyl-4-bromobicyclo[3.3.1]non-2-ene (**14**). Reaction of **14** with potassium *tert*-butoxide in *tert*-butyl alcohol proceeds smoothly to provide **15** as the only volatile product. By this sequence of reactions, **15** was obtained from acid **7** in an overall isolated yield of 28%.

In order to firmly establish the carbon skeleton of **15**, it was converted to the parent hydrocarbon, tricyclo[3.3.1.0^{2,7}]-nonane (**1**), by the sequence of reactions summarized in Scheme II. Oxidation of methyl ketone **15** with sodium hypobromite gives 1-carboxytricyclo[3.3.1.0^{2,7}]non-3-ene (**16**) in quantitative yield. The infrared spectrum of **16** shows a broad absorption from 3500 to 2750 cm^{-1} and a carbonyl absorption at 1695 cm^{-1}. The ^{13}C NMR spectrum of **16** contains ten carbon resonances and features singlets at δ 181.9 and 46.1 which are assigned to the carboxylate carbon and the quaternary carbon at C-1, respectively. Catalytic hydrogenation of **16** affords the corresponding saturated acid **17** in 95% yield. Treatment of the sodium salt of **17** with oxalyl chloride provides **18**. The acid chloride was not purified but rather was reacted immediately with *tert*-butyl hydroperoxide to give *tert*-butyl perester **19**. Subsequent pyrolysis of the perester at 155 °C by the method of Langhals and Ruechardt[10] gives **1** in an overall isolated yield of 16% from acid **17**. Consistent with the presence of a plane of symmetry in **1**, the ^{13}C NMR spectrum of **1** contains only seven signals. Moreover, one of the four signals for methylene carbons is twice as intense as the others and one of the three signals for methine carbons is twice as intense as the others.

In view of the numerous reported transformations of 1-carboxyadamantane,[11] it is apparent that acids **16** and **17** offer convenient entry points for the preparation of a variety of bridgehead substituted tricyclo[3.3.1.0^{2,7}]nonanes.

Experimental Section

Melting points were obtained in sealed capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers. Proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60 MHz spectrometers and are referenced to an internal standard of tetramethylsilane. Apparent splittings are reported in all cases. Carbon magnetic resonance spectra were taken at an operating frequency of 22.63 MHz on a Brüker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data acquisition system and are referenced to an internal standard of tetramethylsilane. Elemental analyses were performed by Microanalysis, Inc., Wilmington, Del.

3-*endo*-Acetylbicyclo[3.3.1]non-6-ene (8). An ethereal solution of methyllithium (80 mL of a 1.65 M solution, ca. 132 mmol) was added dropwise to a vigorously stirred solution of 3-*endo*-carboxybicyclo[3.3.1]non-6-ene[5] (9.8 g, 59 mmol) in anhydrous ether at 0 °C at such a rate that the temperature of the reaction mixture did not exceed 5 °C. Following this addition, the reaction was stirred at 0 °C for 30 min and at room temperature for 4 h. The reaction was quenched by slowly pouring the reaction mixture into a saturated solution of ammonium chloride. The aqueous layer was separated and extracted with ether (4 × 50 mL). The combined ether layers were washed with 5% aqueous sodium bicarbonate (4 × 50 mL; acidification of the combined basic washes afforded a 300 mg recovery of unreacted starting material) and water (2 × 50 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a yellow liquid. Vacuum distillation of this material gave 7.9 g (84% yield) of ketone 8 as a colorless liquid: bp 70–73 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 5.71–5.18 (br m, 2 H, -CH=CH-) and 2.68–1.28 (br m, 14 H, containing an acetyl methyl singlet at δ 2.05); ^{13}C NMR ($CDCl_3$) δ 211.1 (C=O), 131.4 (C-6 or C-7), 131.2 (C-6 or C-7), 46.3 (C-3), 33.1 (t), 32.9 (t), 31.7 (t), 31.1 (t), 29.8 (C-1 or C-5), 28.7 (CH_3), and 27.5 (C-1 or C-5); ν (CCl_4) 3020, 2925, 2905, 2855, 1704, 1430, 1350, 1210, 1190, 1170, and 1105 cm^{-1}.

The semicarbazone derivative of 8 was prepared according to the procedure outlined by Fieser,[12] mp 209–210 °C.

Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.13; H, 8.65; N, 18.99. Found: C, 64.89; H, 8.87; N, 18.87.

3-*exo*-Acetylbicyclo[3.3.1]non-6-ene (9). A. A stirred solution of 8 (2.0 g, 6.1 mmol) and *p*-toluenesulfonic acid monohydrate (150 mg) in benzene (200 mL) was heated at reflux for 48 h. The reaction mixture was then cooled to room temperature and diluted with ether (100 mL). The resulting soltuion was washed successively with 5% aqueous sodium bicarbonate (4 × 25 mL), water (2 × 25 mL), and saturated aqueous sodium chloride (25 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a viscous yellow liquid which was purified by vacuum distillation to give 9 (1.34 g, 67% yield) as a colorless liquid. Further purification of 9 by GLC (5 ft × 0.25 in. Carbowax column, 225 °C) provided an analytical sample: ^{1}H NMR ($CDCl_3$) δ 6.10–5.57 (br m, 2 H, -CH=CH-) and 3.19–1.00 (br m, 14 H, containing an acetyl methyl singlet at δ 2.10); ^{13}C NMR δ ($CDCl_3$) 213.7 (C=O), 131.7 (C-6 or C-7), 130.8 (C-6 or C-7), 45.1 (C-3), 36.8 (t), 33.6 (t), 32.9 (C-1 or C-5), 32.2 (t), 30.3 (C-1 or C-5), 29.2 (CH_3), and 28.0 (t); ν (CCl_4) 3025, 2930, 2905, 2855, 2835, 1710, 1455, 1435, 1350, 1285, 1240, 1235, and 1170 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.58; H, 9.64.

Ketone 9 was recovered unchanged when it was submitted to the identical reaction conditions previously employed for 8 → 9.

B. A neat sample of 8 (175 mg, 1.1 mmol) was heated at 200–205 °C in a sealed ampule for 24 h. The infrared and ^{1}H NMR spectra of the crude product were identical with those previously obtained for 9 which had been generated by the acid-catalyzed epimerization of ketone 8. Particularly diagnostic for 8 vs. 9 is the chemical shift of the olefinic protons in the ^{1}H NMR spectra of these ketones which appear at δ 5.71–5.18 in 8 and at δ 6.10–5.57 in 9. Ketone 8 was recovered unchanged when it was heated at 100 °C for 24 h. On the other hand, ^{1}H NMR analysis of the crude reaction product obtained from heating 8 at 125 °C for 36 h indicated a ca. 1:1 ratio of 8 and 9.

C. A solution of 8 (200 mg, 1.2 mmol) in anhydrous *tert*-butyl alcohol (10 mL) was added dropwise to a freshly prepared solution of potassium (75 mg, 1.92 mmol) in anhydrous *tert*-butyl alcohol (75 mL). The resulting solution was stirred at room temperature for 12 h. The reaction mixture was then poured into a slurry of ice and water (500 mL) and extracted with pentane (4 × 100 mL). The combined pentane extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a pale yellow liquid (90 mg). Examination of both the ^{1}H NMR and IR spectra of the crude product indicated that complete epimerization had occurred to give 9.

3-*exo*-Acetylbicyclo[3.3.1]nonane (10). A. A mixture of 9 (250 mg, 1.5 mmol), 10% palladium on charcoal (25 mg), and ethanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 25 h. At this point the catalyst was removed by suction filtration through Celite. Evaporation of the solvent from the filtrate at reduced pressure gave crude 10 (242 mg, 96% yield) as a colorless liquid. GLC analysis (10 ft × 0.25 in. SE-30 column, 175 °C) indicated the presence of a single component. Purification by GLC (above conditions) afforded an analytical sample of 10: ^{1}H NMR ($CDCl_3$) δ 3.42–2.70 (br m, 1 H, $CHCOCH_3$) and 2.16–1.35 (br m, 17 H, which contains an acetyl methyl singlet at δ 2.08); ν (CCl_4) 2930, 2860, 1710, 1465, 1440, 1350, 1295, 1245, 1235, and 1165 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.42; H, 11.01.

B. A neat sample of 20 (100 mg, 0.6 mmol) was heated at 200–205 °C in a sealed ampule for 24 h. Vacuum distillation of the crude product with a molecular still provided 10 (65 mg, 65% yield) as a colorless oil. The IR spectrum of this material was identical with that of 10 obtained by procedure A.

3-*exo*-Acetoxybicyclo[3.3.1]nonane (11). A solution of ketone 10 (100 mg, 0.6 mmol) in chloroform (3 mL) was added to a stirred solution of 85% *m*-chloroperbenzoic acid (500 mg, ca. 2.4 mmol) in chloroform (20 mL) and the reaction mixture was stirred at room temperature for 24 h. At this point the excess peracid present was destroyed by the addition of 10% aqueous sodium sulfite solution until a negative starch–iodide test was obtained. The reaction mixture was then diluted with ether (100 mL) and washed with 5% aqueous sodium bicarbonate (4 × 25 mL) and water (2 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to give 108 mg (100% yield) of crude 11. Purification by GLC (10 ft × 0.25 in. SE-30 column, 200 °C) afforded pure acetate 11 as a colorless liquid. The IR and ^{1}H NMR spectra of this material were identical with those previously reported for 11.[7]

3-*exo*-Acetylbicyclo[3.3.1]non-6-ene Ethylene Ketal (12). A mixture of 8 (8.28 g, 50.4 mmol), ethylene glycol (3.76 g, 60.5 mmol), *p*-toluenesulfonic acid monohydrate (400 mg), and anhydrous benzene (180 mL) was stirred at reflux under a nitrogen atmosphere for 36 h. During this time, the water generated by the reaction was collected in a Dean-Stark trap. The reaction was cooled to room temperature and washed with 10% aqueous sodium hydroxide (3 × 50 mL), water (4 × 25 mL), and saturated sodium chloride (25 mL). After the organic layer had been dried over anhydrous magnesium sulfate, the solvent was evaporated at reduced pressure to give the crude ketal as a viscous, yellow liquid. Purification by vacuum distillation provided pure 12 as a colorless liquid (8.33 g, 79% yield): bp 75–78 °C (0.1 mm); ^{1}H NMR (CCl_4) δ 5.93–5.73 (m, 2 H, -CH=CH-), 3.87 (br s, 4 H, $-OCH_2CH_2O-$), and 2.67–0.98 (br m, 14 H, containing a methyl singlet at δ 1.15); ν (CCl_4) 3020, 2980, 2925, 2830, 1440, 1380, 1240, 1220, 1110, and 1055 cm^{-1}.

7-*exo*-Acetyl-4-bromobicyclo[3.3.1]non-2-ene Ethylene Ketal (13). A vigorously stirred mixture of 12 (5.24 g, 25.1 mmol), purified *N*-bromosuccinimide (4.5 g, 25.3 mmol), benzoyl peroxide (50 mg), and carbon tetrachloride (300 mL) was heated for 2 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and the succinimide present was removed by suction filtration. The filtrate was evaporated at reduced pressure to afford crude bromo ketal 13 as a colorless liquid (7.12 g, ca. 99% yield): ^{1}H NMR (CCl_4) δ 6.30–5.67 (br m, 2 H, -CH=CH-), 4.65 (br d, J = 4 Hz, 1 H, CHBr), 3.88 (br s, 4 H, $-OCH_2CH_2O-$), and 2.71–0.97 (br m, 12 H, containing a methyl singlet at δ 1.14); ν (CCl_4) 3035, 2980, 2935, 2880, 1460, 1445, 1375, 1240, 1220, 1165, 1140, 1055, and 1040 cm^{-1}.

Due to the unstable nature of 13, no attempt was made at further purification and the crude material was immediately converted to 14.

7-*exo*-Acetyl-4-bromobicyclo[3.3.1]non-2-ene (14). A stirred solution of 13 (7.12 g, 24.8 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg) in anhydrous acetone (175 mL) was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and the acetone was evaporated at reduced pressure. The residue was dissolved in ether (200 mL) and washed consecutively with 5% aqueous sodium bicarbonate (3 × 25 mL) and water (2 × 25 mL). The organic layer was then dried over anhydrous magnesium sulfate and treated with activated carbon. Evaporation of the ether at reduced pressure gave a dark brown liquid (6.10 g). Analysis of the crude product by ^{1}H NMR indicated the presence of 5.83 g of bromo ketone 14. This represents an overall yield of 95% from ketal 12 to 14. The crude bromo ketone was vacuum distilled through a 8 cm Vigreux

column to provide **14** as a pale yellow liquid (5.39 g, 89% yield): bp 100–105 °C (0.1 mm); ^{1}H NMR (CCl_4) δ 6.35–5.72 (br m, 2 H, –CH=CH–), 4.68 (br d, J = 4 Hz, 1 H, CHBr), and 2.90–1.29 (br m, 12 H, containing an acetyl methyl singlet at δ 2.05); ν (CCl_4) 3035, 2930, 2860, 1712, 1455, 1440, 1350, 1175, and 1160 cm^{-1}.

1-Acetyltricyclo[3.3.1.0^{2,7}]non-3-ene (15). A solution of **14** (1.6 g, 6.6 mmol) in dry *tert*-butyl alcohol (5 mL) was added dropwise to a stirred solution of potassium (270 mg, 6.9 mmol) in dry *tert*-butyl alcohol (50 mL, freshly distilled from sodium) which was maintained under a nitrogen atmosphere. An immediate pale yellow precipitate resulted. The reaction was stirred at reflux for 17 h, cooled to room temperature, and poured into a slurry of ice and water (250 mL). The aqueous phase was extracted with pentane (4 × 100 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a pale yellow liquid (940 mg). Purification of this material by vacuum distillation provided pure **15** (510 mg, 48% yield) as a colorless liquid: bp 73–76 °C (0.03 mm); ^{1}H NMR ($CDCl_3$) δ 6.97–6.62 and 6.37–6.03 (each complex t, J = 7.5 Hz, each 1 H, –CH=CH–) and 3.32–0.86 (br m, 12 H, containing an acetyl methyl at δ 1.86); ν (CCl_4) 3050, 2945, 2865, 1701, 1445, 1360, 1285, 1270, 1235, 1225, 1100, and 1090 cm^{-1}.

The semicarbazone derivative of **15** was prepared according to the procedure outlined by Fieser,[12] mp 198–200 °C.

Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.46; H, 7.90; N, 19.19.

1-Carboxytricyclo[3.3.1.0^{2,7}]non-3-ene (16). A freshly prepared solution of sodium hypobromite (formed by the addition of 3.4 g of bromine to a solution of 3.3 g of sodium hydroxide in 30 mL of dioxane and 19 mL of water at 0 °C) was added rapidly to a vigorously stirred ice-cold solution of **15** (850 mg, 5.2 mmol) in dioxane (50 mL) and water (17.5 mL). As the reaction was stirred at 0 °C for 3 h, the color of the reaction mixture gradually changed from pale yellow to colorless. The reaction was quenched by the addition of a solution of sodium sulfite (1.2 g) in water (10 mL). The reaction mixture was then diluted with 10% aqueous sodium hydroxide (60 mL) and the aqueous phase was separated and washed with ether (2 × 50 mL). The aqueous layer was subsequently acidified with hydrochloric acid and the resulting precipitates were extracted into ethyl acetate (4 × 25 mL). The ethyl acetate extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided **16** (849 mg, 99% yield) as a waxy white solid which proved to be homogeneous by GLC analysis (10 ft × 0.25 in. SE-30 column, 175 °C; 10 ft × 0.25 in. DC-550 column, 175 °C). Acid **16** showed: ^{1}H NMR ($CDCl_3$) δ 11.53 (br s, 1 H, CO_2H), 7.00–6.60 and 6.36–5.96 (each complex t, J = 7 Hz, each 1 H, –CH=CH–), and 3.58–0.85 (br m, 9 H); ^{13}C NMR ($CDCl_3$) tentative assignments δ 181.9 (C=O), 140.6 (C-3 or C-4), 126.4 (C-3 or C-4), 46.1 (C-1), 40.4 (C-2), 39.7 (t), 35.1 (t), 31.9 (t), 31.5 (d), and 29.6 (d); ν (CCl_4) 3500–2750 (br), 3050, 2945, 2860, 1695, 1445, 1420, 1295, 1245, 1230, 1205, and 1120 cm^{-1}.

Acid **16** proved to be thermally labile under GLC conditions. Catalytic hydrogenation of **16** afforded **17** which could be completely characterized.

1-Carboxytricyclo[3.3.1.0^{2,7}]nonane (17). A mixture of **16** (100 mg, 0.6 mmol), 10% palladium on charcoal (20 mg), and ethanol (5 mL) was stirred under an atmosphere of hydrogen at room temperature for 15 h. The reaction mixture was then filtered to remove the catalyst and the ethanol was evaporated at reduced pressure to give a yellow liquid (97 mg, 95% yield) which by GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) contained a single component. Isolation by GLC (above conditions) provided **17** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 11.40 (br s, 1 H, CO_2H) and 2.67–1.20 (br m, 13 H); ν (CCl_4) 3400–2750 (br), 2935, 2860, 1696, 1460, 1420, 1335, 1290, 1130, and 1085 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.99; H, 8.46.

Tricyclo[3.3.1.0^{2,7}]nonane (1). A stirred mixture of acid **17** (3.2 g, 19.3 mmol) in 50% aqueous methanol (300 mL) was titrated to a phenolphtalein end point with 10% aqueous sodium hydroxide. After stirring the reaction mixture at room temperature for 3 h, the solvent was evaporated at reduced pressure and the residue was heated at 70 °C (0.01 mm) for 8 h. The resulting dry sodium salt of **17** was suspended in a mixture of anhydrous benzene (200 mL) and anhydrous pyridine (2.9 g), cooled to 0 °C, and stirred as oxalyl chloride (8 mL, 96 mmol) was added dropwise. After addition was complete, the reaction mixture was stirred at 0 °C for 15 min and at room temperature for 15 min. The resulting precipitates were filtered and washed with anhydrous benzene (2 × 50 mL). The filtrate and washings were combined and the solvent was evaporated at reduced pressure to provide **1-tricyclo[3.3.1.0^{2,7}]nonanoyl chloride** (18) as an oil: ν (neat) 1790 cm^{-1}.

A solution of the crude acid chloride in methylene chloride (70 mL) was then added to an ice-cooled stirred mixture of *tert*-butyl hydroperoxide (2.75 g, ca. 30 mmol) and anhydrous pyridine (2.3 g, 29 mmol) in methylene chloride (180 mL). The dropwise addition required 1 h. The reaction mixture was stored at 0 °C for 9 h. At this point the reaction mixture was washed successively with water (2 × 50 mL), 10% aqueous sulfuric acid (2 × 50 mL), 5% aqueous sodium bicarbonate (2 × 50 mL), and water (50 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent at room temperature under reduced pressure provided *tert*-butyl perester **19** as a pale yellow oil (2.25 g): ν (neat) 1745 cm^{-1}.

A solution of crude **19** in ethyl phenylacetate (30 mL) was heated at 155 °C for 2 h according to the method of Langhals and Ruechardt.[10] Methanol (10 ml) and 45% aqueous sodium hydroxide (80 g of sodium hydroxide dissolved in 100 mL of water) were added to the cooled reaction mixture and it was refluxed for 4 h under a nitrogen atmosphere. At this point the reaction mixture was cooled to room temperature and diluted with water (200 mL). The mixture was extracted with pentane (4 × 100 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate. Removal of the solvent by atmospheric distillation afforded the crude hydrocarbon as a viscous yellow oil (380 mg, 16% yield) which by GLC analysis (10 ft × 0.25 in. SE-30 column, 140 °C) was homogeneous and contained no unreacted starting material. The hydrocarbon was purified by repeated sublimation at room temperature using a water aspirator to give pure **1** as a waxy, white solid: mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 2.45–1.05 (complex m); ^{13}C NMR ($CDCl_3$) δ 38.5 (t), 35.1 (C-1 and C-7), 35.0 (C-6 and C-9), 33.3 (d), 29.5 (t), 26.4 (d), 19.6 (t); ν ($CDCl_3$) 2925, 2860, 1450, 1340, 1310, 1270, 1230, 1205, and 1140 cm^{-1}.

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.41; H, 11.58.

3-*endo*-Acetylbicyclo[3.3.1]nonane (20). An ethereal solution of methyllithium (4.5 mL of a 1.65 M solution, ca. 7.4 mmol) was added dropwise to a vigorously stirred solution of 3-carboxybicyclo[3.3.1]nonane[13] (**22**) (495 mg, 3 mmol) in anhydrous ether at 0 °C at such a rate that the temperature of the reaction mixture did not exceed 5 °C. Workup of the reaction mixture followed the procedure described for **7** → **8**. Evaporation of the solvent at reduced pressure afforded 460 mg (92% yield) of crude **20** as a pale yellow liquid. Analysis of the crude reaction mixture by GLC (10 ft × 0.25 in. SE-30 column, 210 °C) showed the presence of a single component. Purification of this material by GLC (above conditions) provided **20** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.76–0.90 (br m, containing an acetyl methyl singlet at δ 2.12); ν (CCl_4) 2930, 2850, 1710, 1460, 1440, 1350, 1250, and 1170 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.69; H, 10.62.

Oxidation of **20** (355 mg, 2.2 mmol) with sodium hypobromite by the procedure described for **15** → **16** gave acid **22** (200 mg, 55% yield). The infrared and ^{1}H NMR spectra of this material were identical with those of **22** obtained from the catalytic hydrogenation of **7**.

3-*endo*-Acetoxybicyclo[3.3.1]nonane (21). A solution of **20** (100 mg, 0.6 mmol) in chloroform (3 mL) was added to a stirred solution of 85% *m*-chloroperoxybenzoic acid (500 mg, ca. 2.4 mmol) in chloroform (20 mL) and the reaction mixture was stirred at room temperature for 48 h. Workup of the reaction mixture followed the procedure described for **10** → **11**. Evaporation of the solvent at reduced pressure provided 95 mg (95% yield) of crude **21**. Purification by GLC (10 ft × 0.25 in. SE-30 column, 200 °C) afforded pure acetate **21** as a colorless liquid. The IR and ^{1}H NMR spectra of this material were identical with those previously reported for **21**.[7]

Acknowledgment. This work was supported by grants from the Research Corporation and the University of Delaware Research Foundation.

Registry No.—**1**, 766-67-6; **7**, 21932-98-9; **8**, 66483-55-4; **8** semicarbazone, 66483-56-5; **9**, 67226-63-5; **10**, 67226-64-6; **11**, 23825-38-9; **12**, 67226-65-7; **13**, 67226-66-8; **14**, 67226-67-9; **15**, 67226-68-0; **15** semicarbazone, 67226-69-1; **16**, 67226-70-4; **17**, 67226-71-5; **17** Na salt, 67226-72-6; **18**, 67226-73-7; **19**, 67226-74-8; **20**, 19489-20-4; **21**, 19490-34-7; **22**, 19489-18-0; ethylene glycol, 107-21-1.

References and Notes

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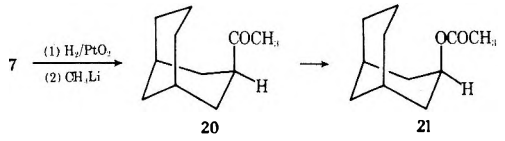
(8) Ketone **10** also can be obtained by heating 3-*endo*-acetylbicyclo[3.3.1]-nonane (**20**) in a sealed ampule at 200–205 °C. Ketone **20** is readily prepared from acid **7**. Catalytic hydrogenation of **7** gives 3-carboxybicyclo[3.3.1]nonane[13] which undergoes reaction with methyllithium to provide **20**. The skeletal framework of **20** and the skeletal position and stereochemistry of the acetyl group in **20** were firmly established by its oxidation with *m*-chloroperbenzoic acid to give the previously reported 3-*endo*-acetoxybicyclo[3.3.1]nonane[7] (**21**).



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(9) Since **8** → **9** is acid-catalyzed, ketone **8** can be converted "directly" to epimerized ketal **12** by reaction of **8** with ethylene glycol containing a trace of *p*-toluenesulfonic acid.
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syn- and *anti*-Tricyclo[4.1.0.0^{2,4}]heptan-5-one

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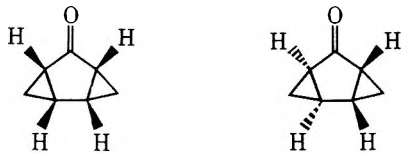
The synthesis, isolation, and spectroscopic characterization of the epimeric ketones *syn*- and *anti*-tricyclo[4.1.0.0^{2,4}]heptan-5-one (**1** and **2**) are described. Two synthetic schemes lead to a nearly equimolar mixture of **1** and **2**, while a third yields **2** almost exclusively. The syn isomer **1** proved much more labile compared to the anti isomer **2**. Complete assignments of protons in the NMR spectra were made possible by a study of lanthanide-induced chemical shift modifications.

The epimeric ketones *syn*- and *anti*-tricyclo[4.1.0.0^{2,4}]-heptan-5-ones (**1** and **2**) are of interest as precursors of the



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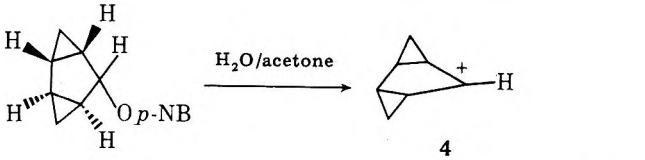
epimeric carbene species *syn*- and *anti*-tricyclo[4.1.0.0^{2,4}]-heptan-5-ylidenes[2] and as precursors of the carbonium ion species *syn*- and *anti*-tricyclo[4.1.0.0^{2,4}]hept-5-yl cations. The anti ketone **2** had earlier been synthesized by Gajewski and Shih and was utilized in an investigation of the properties of anti cation **4** as generated by the solvolysis of **3**.[3] **3** was found



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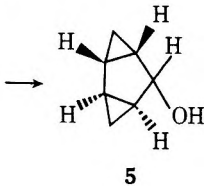

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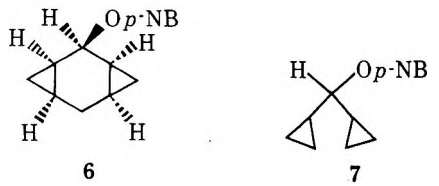
to be significantly less reactive than the model compounds **6** and **7**. We wish to report the details of the synthesis of the syn ketone **1** along with the total spectroscopic characterization



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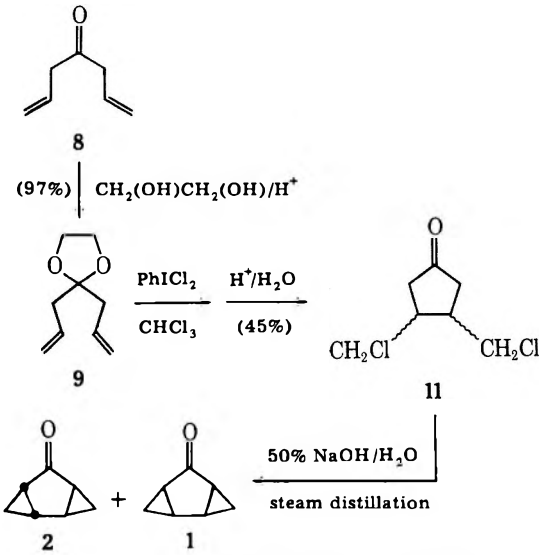
Scheme I

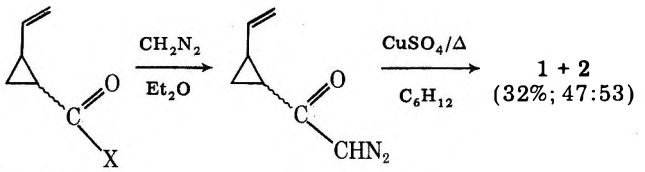


of both the syn and anti isomers and a discussion of their relative chemical properties.

Synthetic Methods. Three synthetic schemes were developed and successfully pursued for the preparation of **1** and **2**. Scheme I began with the known diallyl ketone **8**.[4] Ketalization and treatment of the ketal **9** with iodobenzene dichloride[5] led, after hydrolysis, to a mixture of *cis*- and *trans*-3,4-bis(chloromethyl)cyclopentanones (**11**). Treatment of **11** with 50% aqueous NaOH followed by steam distillation resulted in a mixture of products which proved to be 52 and 48% *syn*- and *anti*-tricyclo[4.1.0.0^{2,4}]heptan-5-one, respectively. Gajewski's synthesis of **2** also involved a cyclization process such as that used to convert **11**.[3] In their final step they converted a pure trans ditosylate into **2**.

Scheme II employed a sequence which appeared to be somewhat more convenient. Drawing on the analogues provided by Doering[6] and Gutsche[7] in performing intramolecular trapping of keto carbenoids by a remote double bond, a se-

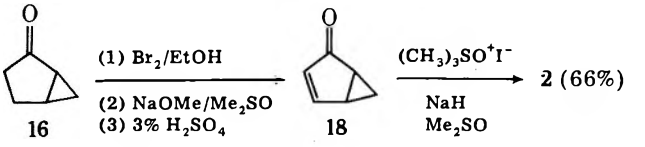
Scheme II



12, X = OEt
13, X = OH
14, X = Cl

15

Scheme III



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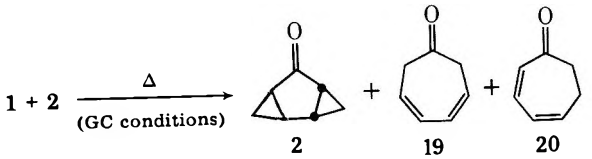
quence was devised utilizing a mixture of *cis*- and *trans*-ethyl 2-vinylcyclopropanecarboxylate (**12**) as starting material.[8] Treatment of acid chloride **14** with ethereal diazomethane afforded a mixture of *cis*- and *trans*-1-diazomethylketo-2-vinylcyclopropanes (**15**) as evidenced by the strong IR band at 2100 cm^{-1} and the diazomethyl singlet at δ 5.31 in the NMR spectrum. Copper-catalyzed decomposition of **15** in refluxing cyclohexane produced a 32% yield of isomeric tricyclic ketones **1** and **2** in a ratio of 47:53.

Scheme III, while not providing a satisfactory route to the syn ketone **1**, did result in an interesting source of **2**. The starting material in Scheme III was bicyclo[3.1.0]hexan-2-one (**16**), which could be synthesized from either 4-tosyloxycyclohexanone[9] or 2-cyclopentenone.[10] Bicyclo[3.1.0]hex-3-en-2-one (**18**) was prepared from **16** employing the procedure of Russell and Stevenson,[11] with some modification. The treatment of **18** with trimethylsulfoxonium ylide afforded **1** and **2** in a ratio of 2:98.

Isolation of the Pure Isomeric Ketones. Detection and isolation of **1** and **2** proved initially troublesome using normal GC. An injection of the isomeric mixture of ketones onto various Carbowax 20M columns at 130–160 °C typically resulted in the isolation of *three* isomeric ketones, none of which proved to be the syn isomer **1**.



2 19 20

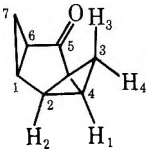
The anti tricyclic ketone **2** was identified by comparison of its ^{1}H NMR spectrum with that reported by Gajewski and Shih.[3] The outstanding feature of this NMR spectrum (100 MHz) is the unsymmetrical two-proton quartet (J = 3.5 Hz) at δ 0.85. The remainder of the spectrum consisted of three two-proton multiplets centered at δ 1.25, 1.56, and 2.08. The IR (1720 cm^{-1}), UV [λ_{max} 287 nm (ϵ 28)], and mass spectra [m/e 108 (M$^+$)] were also confirmative of the structure. The other two products proved to be 2,4- and 3,5-cycloheptadienones, which were recognizable by the four-proton multiplet at δ 3.00 for the 3,5 isomer.[12] These products were accounted for by an acid-promoted rearrangement of the entire syn ketone and part of the anti ketone. Previous work by Borg and Kloosterziel had shown that the cycloheptadienones were interconvertible in the temperature range of 60–100 °C via a facile 1,5-hydrogen shift, resulting in an equilibrium mixture dominated by the 2,4 isomer.[12]

Isolation of analytically pure **1** and **2** was accomplished by the use of an *alkaline* column (10% Carbowax 20M) using 3.5% KOH to effectively remove active sites from the inert support, typically Chromosorb P (regular). Whereas liberal injections of ammonia had not proved successful, the KOH-coated column allowed for almost quantitative separation and isolation of **1** and **2** in the temperature range of 130–165 °C. However, at temperatures above 180 °C, almost complete destruction of the syn isomer was observed.

The *syn*-tricyclo[4.1.0.0^{2,4}]heptan-5-one gave rise to four complex two-proton multiplets in its 100 MHZ NMR spectrum at δ 0.76, 1.50, 1.78, and 2.18. The multiplets at δ 1.50 and 1.78 were overlapping, a feature which readily distinguishes **1** from **2**. Its IR (1700 cm^{-1}), UV [λ_{max} 283 nm (ϵ 70)], and mass spectra [*m/e* 108 (M$^+$)] were also consistent with the structure.

Silica gel chromatography conveniently afforded separation of larger quantities of **1** and **2**. Both **1** and **2** could readily be converted to their tosylhydrazones, with **1** being converted in 83% and **2** in but 31% yield.

Lanthanide-Induced Chemical Shift Studies. A concluding aspect of analysis of **1** and **2** derived from an attempt to assign their various NMR proton absorptions. Employing Eu(fod)$_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium(III), lanthanide-induced shifts produced some rather interesting spectral changes, the most interesting of which demonstrated that the two protons adjacent to the carbonyl function (α-methine cyclopropyl protons) in both **1** and **2** were *not* located farthest downfield in the NMR spectra. It appeared that the protons most deshielded in these systems were the two protons located at C$_1$ and C$_2$, the β-methine cyclopropyl protons. Further, calculations of the agreement factor R[13] for the four types of protons present afforded values of 0.16 and 0.23 for **1** and **2**, respectively. Also



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of interest is the fact that the endo protons at C$_3$ and C$_7$ in **2** lie 0.65 ppm farther upfield than the endo protons of **1**.

The leap-frog effect which occurs when Eu(fod)$_3$ is added to **1** or **2** in CDCl$_3$ is demonstrated by the extrapolated values of ΔEu_i (where $Eu/1$ or **2** = 1). For **1**, ΔEu_i (hertz downfield from Me$_4$Si at 60 MHz) = 790 (H$_1$), 373 (H$_2$), 413 (H$_3$), and 256 (H$_4$); for **2**, ΔEu_i (Hz) = 740 (H$_1$), 395 (H$_2$), 406 (H$_3$), and 300 (H$_4$). These NMR observations of **1** and **2** show analogy to the case of bicyclo[3.1.0]hex-3-ene-2-one (**18**), where NMR work by Hasty has shown that the α-methine cyclopropyl proton appeared at δ 2.38.[14]

The significantly greater sensitivity of the syn ketone to acid-catalyzed isomerization is a strong indication that the carbonium ion with the syn configuration is either more easily formed or that it *rearranges* more rapidly than the anti carbonium ion, which has already been examined by Gajewski and Shih. In contrast, we found that the carbenes generated by thermolysis of the tosylhydrazone sodium salts of **1** and **2** showed remarkably similar behavior.[2]

Experimental Section

IR spectra were recorded on Perkin-Elmer Model 137 or 437 spectrometers. ^{1}H NMR spectra were obtained using Varian Model A-60-A and Xl-100 spectrometers. Mass spectra were obtained using either a Hitachi Perkin-Elmer RMU-6E or an AEI MS 30 mass spectrometer. UV spectra were obtained on a Cary 15 spectrometer and elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Ga. GC work was carried out using a Varian Aerograph Model A-90-P3 gas chromatograph.

2,2-Diallyl-1,3-dioxolane (9). A solution of 6.95 g (0.0631 mol) of hepta-1,6-dien-4-one (**8**)[4] in 70 mL of benzene was mixed with 5.15 g (0.0830 mol) of ethylene glycol and 0.05 g of *p*-toluenesulfonic acid

monohydrate in a 200 mL round-bottom flask. The flask was fitted with a Dean-Stark trap and a condenser (equipped with a drying tube). The mixture was refluxed until 1.1 mL of water had been collected (97% of the theoretical amount). The cooled reaction mixture was washed with 20 mL of 10% sodium hydroxide solution followed by five 10-mL washes with water. The benzene extract was dried over anhydrous K_2CO_3 and the benzene removed by rotary evaporation. The residual liquid was distilled at 20 mm, affording 4.88 g (0.0316 mol) of **9** (50%): bp 75–76 °C; IR (film) 3040, 3030, 2875, 1645, 1430, 1320, 1300, 1285, 1265, 1240, 1200, 1175, 1140, 1115, 1081, 1040, 1000, 990, 920 cm^{-1}; NMR ($CDCl_3$) δ 2.39 (d with splitting, J = 7 Hz, 4 H), 3.90 (s, 4 H), 4.81–5.28 (AB m, terminal vinyl H, 4 H), 5.47–6.10 (m, 2 H); MS m/e 154 (M^+), 113 ($M^+ - C_3H_5$, major peak).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.35; H, 9.11.

***cis*- and *trans*-3,4-Bis(chloromethyl)cyclopentanone (11).** A mixture of 6.75 g (0.0437 mol) of **9** and 12.1 g (0.0440 mol) of iodobenzene dichloride[5] in 75 mL of chloroform was heated at reflux for 2 h under a slow stream of nitrogen. The chloroform solvent was removed by rotary evaporation, affording a slightly colored mixture containing iodobenzene and crude *cis*- and *trans*-7,8-bis(chloromethyl)-1,4-dioxaspiro[4.4]nonane. The iodobenzene was removed at 0.25 mm while heating the flask to 45 °C. Short-path distillation of the product [bp 88–95 °C (0.25 mm)] afforded 6.80 g (0.0302 mol, 69%) of a brown tinted product.

The crude product (6.75 g, 0.0300 mol) was dissolved in 70 mL of 3:1 ethanol–water containing 200 mg of *p*-toluenesulfonic acid. The solution was heated at 35–38 °C for 24 h. The solution was poured into 500 mL of a saturated Na_2CO_3 solution and extracted with three 200-mL portions of ether. The combined ethereal extracts were washed with water until neutral, followed by a final washing with 100 mL of saturated sodium chloride solution. The ethereal extract was dried over sodium sulfate and concentrated by rotary evaporation, affording 5.11 g of an orange oil. The oil was fractionated through a short-path distilling head (hydroquinone stabilizer), affording the desired dichloro ketone **11**: 2.42 g (0.0134 mol, 45%); IR (film) 2970, 2920, 1755, 1445, 1410, 1370, 1275, 1170, 1100, 770, 735 cm^{-1}; NMR ($CDCl_3$) δ 2.17–2.58 (m, 4 H), 2.58–3.21 (m, 2 H), 3.57–3.80 (overlapping d, $J_{cis} = J_{trans}$ = 6 Hz, 4 H); MS m/e 185 ($M^+ + 4$; 11.1% of M^+), 183 ($M^+ + 2$; 66.2% of M^+), 181 (M^+), 103 ($M^+ - C_3H_7Cl$, major peak).

***syn*- and *anti*-Tricyclo[4.1.0.0^{2,4}]heptan-5-ones (1 and 2). Method A.** A 2.42-g (0.0134 mol) mixture of crude *cis*- and *trans*-**11** was added dropwise to a well-stirred 215 mL 50% sodium hydroxide solution in a 250 mL three-neck flask equipped with a short-path distilling head and a steam inlet (gas bubbler). After stirring for 30 min (reaction mixture had become black), a slow stream of steam was introduced accompanied by gradual heating of the dark reaction mixture to 150 °C (oil bath). The reaction mixture was heated for a minimum of 2 h, periodically introducing 3–4 mL of water to maintain the solvent level. The oil–water distillate was extracted with three 100-mL portions of ether, and the ethereal extract was dried over $MgSO_4$. Concentration by rotary evaporation afforded a light yellow oil (1.15 g), which was distilled to afford 0.83 g of a colorless oil, boiling at 37–42 °C (0.25 mm). The oil (0.00769 mol, 57%) proved to be a clean mixture of the syn (52%) and anti (48%) tricyclic ketones **1** and **2** by GC on a 10 ft × 0.25 in, 10% Carbowax 20M column containing 3.5% KOH (column, 150 °C; He flow, 100 mL/min). The retention times were 15.7 (anti) and 19.6 min (syn). Anti isomer **2**: mp 41.0–42.0 °C (sealed capillary); IR (CCl_4) 2980, 1790 (sh), 1720 (s), 1440, 1340, 1925, 1190, 1145, 1100 (w), 1075 (w), 1050, 1030, 955 (s), 935 (s), 860 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 0.85 (unsymmetrical q, J = 3.5 Hz, 2 H), 1.25 (m, 2 H), 1.56 (m, 2 H), 2.08 (m, 2 H); UV (ethanol) λ_{max} 287 nm (ε 28); MS m/e 108 (M^+), 79 ($M^+ - COH$, major peak).

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.45.

Syn isomer **1**: IR (film) 2980, 1795 (sh), 1700 (s), 1455, 1313 (sh), 1285, 1185, 1150 (w), 1085 (w), 1040, 1015, 950, 940, 925 (w), 910, 825, 800 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 0.76 (m, 2 H), 1.50 and 1.78 (two overlapping multiplets, 4 H), 2.18 (m, 2 H); UV (ethanol) λ_{max} 283 nm (ε 70); MS m/e 108 (M^+), 79 ($M^+ - COH$, major peak).

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.60; H, 7.53.

***cis*- and *trans*-1-Diazomethylketo-2-vinylcyclopropanes (15).** A solution of 25.8 g (0.460 mol) of potassium hydroxide in 43 mL of water, 150 mL of diethylene glycol monoethyl ether, and 35 mL of ether was placed in a 500 mL Claisen flask equipped with a dropping funnel, a condenser, and two 500 mL Erlenmeyer receivers employing the basic set-up described for diazomethane generation.[15] The flask was heated at 65–70 °C in a water bath while a 92.5-g (0.432 mol) solution of Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; Aldrich) in 450 mL of ether was added dropwise over a period of 90 min. The ethereal diazomethane (~12.9 g, 0.307 mol) was dried over KOH for 90 min at 0 °C. A solution of cis and trans acid chlorides **14** (10.0 g, 0.0763 mol)[8] in 20 mL of ether was added quickly dropwise to the dried ethereal diazomethane, and the resulting solution was allowed to stir overnight at 25 °C. The yellow ether solution was concentrated by rotary evaporation, giving an orange-yellow oil (~10.0 g, 0.0735 mol) which was employed directly in the next step: IR (film) 3030, 2940, 2100 (s), 1720, 1640 (s), 1440, 1390 (s), 1325 (s), 1205, 1180, 1165 (s), 1100 (s), 1075 (s), 1040, 995, 965, 910 (s), 885, 840, 815, 785, 770, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.75–2.28 (two overlapping m, 4 H), 4.77–5.84 (m, vinyl H, 3 H), 5.31 (s, diazomethyl H, 1 H).

***syn*- and *anti*-Tricyclo[4.1.0.0^{2,4}]heptan-5-ones (1 and 2). Method B.** The crude diazo ketone **15** (10.0 g, 0.0735 mol) was dissolved in 100 mL of cyclohexane and added dropwise over a period of 2 h to a refluxing slurry of 400 mL of cyclohexane and 25 g of anhydrous $CuSO_4$. Upon completion of the addition and further stirring for 1 h under reflux, the slurry was filtered and concentrated via rotary evaporation to afford an orange-red oil. The oil was fractionated (short-path column), giving a fraction (slightly yellow) boiling at 35–44 °C (0.5 mm) and weighing 2.95 g. NMR spectral inspection indicated that the distillate was composed of the desired **1** and **2** contaminated with byproducts possessing the vinylcyclopropane skeleton. Preparative GLC on the above-mentioned KOH-treated column afforded analytically pure samples of the isomeric tricyclic ketones. Column chromatography on silica gel (described below) afforded 1.01 g (0.00935 mol) of separated **1** and **2** (32% from the cis acid chloride). The syn/anti ratio was 47:53.

Purification and Separation of 1 and 2. A crude 7.50-g mixture (distillate from several runs) of **1** and **2** obtained from reaction method B (diazo ketone route) was chromatographed on 200 g (56 cm column height) of silica gel (MCB, G. 62) by eluting (dropping rate, 15 drops/min) with ~900–950 mL of carbon tetrachloride, which both removed major impurities and effected the separation of **1** and **2**. The faster moving syn isomer was stripped from the column by elution with 600 mL of 1:1 carbon tetrachloride–methylene chloride followed by ~400 mL of methylene chloride, which served as a transition solvent between **1** and **2** (the use of methylene chloride required monitoring of the eluent by GC). The appearance of the anti isomer was accompanied by elution with ether, which flushed the slower moving isomer from the column. Final purification of the separated isomers was achieved by short-path distillation, which removed traces of colored materials. The syn distillate proved to be absolutely free of the anti isomer, while the anti distillate contained 2.3% of the syn isomer (by GC). The syn/anti distribution was 1.20 g:1.36 g (47:53). The syn/anti mixtures obtained from reaction method A [bis(chloromethyl) ketone route] were separated in the same manner; a final distillation was found to be unnecessary since the distilled starting mixture of isomers was cleaner than the mixture obtained from method B.

Eu(fod)$_3$ Shifts in the ^{1}H NMR Spectra of *syn*- and *anti*-Tricyclo[4.1.0.0^{2,4}]heptan-5-ones. Proton Assignment. Treatment of 0.8-mL deuteriochloroform solutions of **1** (0.0470 g, 4.35 × 10^{-4} mol) and **2** (0.0789 g, 7.31 × 10^{-4} mol) with Eu(fod)$_3$ in varying molar ratios produced interesting lanthanide-induced shifts in the 60 MHz ^{1}H NMR spectra. Assuming the lanthanide atom to lie at a 3.0 Å distance from the oxygen atom (of each respective isomer) in the plane bisecting each system, the various lanthanide–proton distances and proton–Eu–C_5 angles were determined manually from a Dreiding model. Rough calculations of the agreement factor R[13] employing shift data at maximum role ratios afforded R = 0.16 for **1** and R = 0.23 for **2**. Based upon these rough calculations of R and the observed lanthanide-induced shifts in the ^{1}H NMR spectra, the proton assignments of **1** and **2** were established for the 100 MHz spectrum as follows. **1**: δ 0.76 (exo H_4), 1.50 (endo H_3), 1.78 (H_1), 2.18 (H_2). **2**: δ 0.85 (endo H_3), 1.25 (exo H_4), 1.56 (H_1), 2.08 (H_2).

***anti*-Tricyclo[4.1.0.0^{2,4}]heptan-5-one (2). Method C.** Oil-free sodium hydride (0.80 g, 0.033 mol) was added to 50 mL of anhydrous Me_2SO (distilled from CaH_2) in a 100 mL three-neck flask equipped with a solid addition funnel, a condenser, a liquid dropping funnel, and a N_2 inlet. To the mixture was added 7.60 g (0.0345 mol) of trimethylsulfoxonium iodide pinchwise. The resulting solution was allowed to stir for 30 min at 25 °C, whereupon 2.81 g (0.0299 mol) of bicyclo[3.1.0]hex-3-en-2-one (**18**)[9,10] in 10 mL of anhydrous Me_2SO was added slowly dropwise. The solution became orange-brown in color and was stirred at 25 °C for 2 h followed by heating at 55–60 °C for 30 min. The solution was poured into 250 mL of H_2O and extracted with three 150-mL portions of ether. The ethereal extracts were washed with 100 mL of saturated NaCl solution and dried over

Na_2SO_4. Filtration and concentration via rotary evaporation of the ether solution afforded an orange oil (2.74 g) which was distilled through a short-path column at 0.25 mm (bp 36–38 °C). A 2.14-g (0.0198 mol, 66%) fraction of **2** (white solid) was obtained which partially clogged the condenser and receiver elbow, mp 40.5–41.5 °C. GC analysis on the KOH-treated column showed the syn/anti ratio to be 2.2:97.8.

Preparation of Tosylhydrazones. The lability of **1** and **2** in the presence of acid precluded acid-catalyzed formation of the respective tosylhydrazones. The respective tosylhydrazones were prepared by stirring equimolar quantities of *p*-toluenesulfonyl hydrazide and the ketone in absolute ethanol (1 g/25 mL) for 21–24 h (25 °C). A notable exception was **1**, which within 5 min after mixing led to the precipitation of the desired tosylhydrazone; the resulting slurry was stirred for only 2 h before workup. The crude tosylhydrazone obtained from **2** upon removal of solvent was first chromatographed on silica gel (methylene chloride eluent) and then recrystallized from ethanol at 0 °C. The tosylhydrazone from **1** required only recrystallization from ethanol. *syn*-Tricyclo[4.1.0.$0^{2,4}$]heptan-5-one tosylhydrazone: 83% yield; mp 176.0–178 °C dec; IR (KBr) 3350, 3150, 1630, 1580 (sh), 1450, 1390, 1370, 1330, 1310, 1295, 1180, 1160 (s), 1085, 1040, 1015, 940, 900, 825, 810, 720, 705 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (m, cyclopropyl methylene H, 4 H), 1.96 (m, cyclopropyl methine H, 4 H), 2.40 (s, CH_3, 3 H), 7.47 (s, –NH, 1 H), 7.58 (AB q, aromatic H, 4 H); MS *m/e* 276 (M^+), 91 ($C_7H_7^+$, major peak).

Anal. Calcd for $C_{14}H_{16}O_2N_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.84; N, 10.19.

anti-Tricyclo[4.1.0.$0^{2,4}$]heptan-5-one tosylhydrazone: 31% yield; mp 132–134 °C dec; IR (KBr) 3350, 3150, 2850, 1590 (sh), 1540, 1480, 1430, 1385, 1335, 1320, 1310, 1300, 1180, 1160 (s), 1085, 1025, 1010, 935, 895, 820, 805, 725, 715, 705 cm^{-1}; NMR ($CDCl_3$) δ 0.52 (m, cyclopropyl endo H, 2 H), 1.03 (m, cyclopropyl exo H, 2 H), 1.70 (m, cyclopropyl methine H, 4 H), 2.40 (s, CH_3, 3 H), 7.27 (s, –NH, 1 H), 7.58 (AB q, aromatic H, 4 H); MS *m/e* 276 (M^+), 91 ($C_7H_7^+$, major peak).

Anal. Calcd for $C_{14}H_{16}O_2N_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.86; N, 10.17.

Registry No.—**1**, 67252-83-9; 1 tosylhydrazone, 67252-84-0; **2**, 28697-20-3; **2** tosylhydrazone, 67252-85-1; **8**, 53859-89-5; **9**, 67194-62-1; *cis*-**11**, 67194-63-2; *trans*-**11**, 67194-64-3; *cis*-**14**, 2183-92-8; *trans*-**14**, 2183-93-9; *cis*-**15**, 67194-65-4; *trans*-**15**, 67194-66-5; **18**, 32264-58-7; *cis*-7,8-bis(chloromethyl)-1,4-dioxaspiro[4.4]nonane, 67194-67-6; *trans*-7,8-bis(chloromethyl)-1,4-dioxaspiro[4.4]nonane, 67194-68-7.

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Chemistry of Carbanions. 33. Use of Intramolecular Alkylation for the Stereospecific Formation of a *cis*-Decalone[1]

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The synthesis of the decalone derivatives **1** and **14** and the related enol acetates **15** and **16** is described. This synthesis utilizes the stereoselective conjugate addition of CH_2=CHMgBr in the presence of a Cu(I) catalyst to form the vinyl ketone **5**. Subsequent addition of HBr in a radical chain reaction followed by regiospecific formation and cyclization of the bromo enolates **12** and **13** formed the desired decalones **1** and **14**.

To continue exploration of the possibility[2] of controlling reaction stereochemistry in polycyclic systems by use of a conformational effect transmitted from a remote bulky substituent, we wished to prepare ketone **1** (Scheme I). We plan to compare the stereochemistry of C-9 alkylation of this ketone **1** with an earlier study[3] of the alkylation of the stereoisomeric ketone **2**. This paper reports a suitable route for the preparation of ketone **1**.

The basic problem in this synthesis was the requirement to establish and maintain the two chiral centers at C-6 and C-10 in the less stable arrangement with the two alkyl groups trans (i.e., one alkyl group axial). Application of a standard Robinson annulation technique to 4-*tert*-butylcyclohexanone (**3**) was clearly inappropriate because equilibration during this process ultimately leads to the more stable ketone **2**.[3] Consequently, we used an alternative procedure[4,5a] in which the ketone **3** was converted to the enone **4** and then allowed to react with CH_2=CHMgBr in the presence of a Cu(I) catalyst (0.1 molar equiv of Me_2SCuBr). This organometallic reagent (CH_2=CHMgBr + 0.1 equiv of Me_2SCuBr) has been found[4b,5a] to react with enones in a manner equivalent to the cuprate, $(CH_2{=}CH)_2CuLi$, that is presently difficult to prepare because of the lack of a commercial source for vinyllithium. By use of these Cu(I) reagents, both methyl and vinyl groups have been found[4,5a] to add to the enone **4** to form mixtures of stereoisomeric ketones (e.g., **5** and **6**) in which the epimers (e.g., **5**) with an axial methyl or vinyl group constitute >90% of the ketone product. We had previously[5a] used a low-temperature recrystallization technique to separate a pure sample of ketone **5a**, the major stereoisomer in the reaction mixture, and have subsequently found that both epimers **5a** and **5b** can be obtained in pure form by low-pressure liquid chromatography. An equilibrium mixture of these two epimers contained ca. 70% of **5a** and ca. 30% **5b**.[4b,5a] Pure samples of the two minor epimeric ketones **6a** and **6b** were also separated by low-pressure liquid chromatography. An equilibrated mixture of these epimers **6** at 25 °C contained 99% of the equatorial isomer **6a** and 1% of the axial isomer **6b**.

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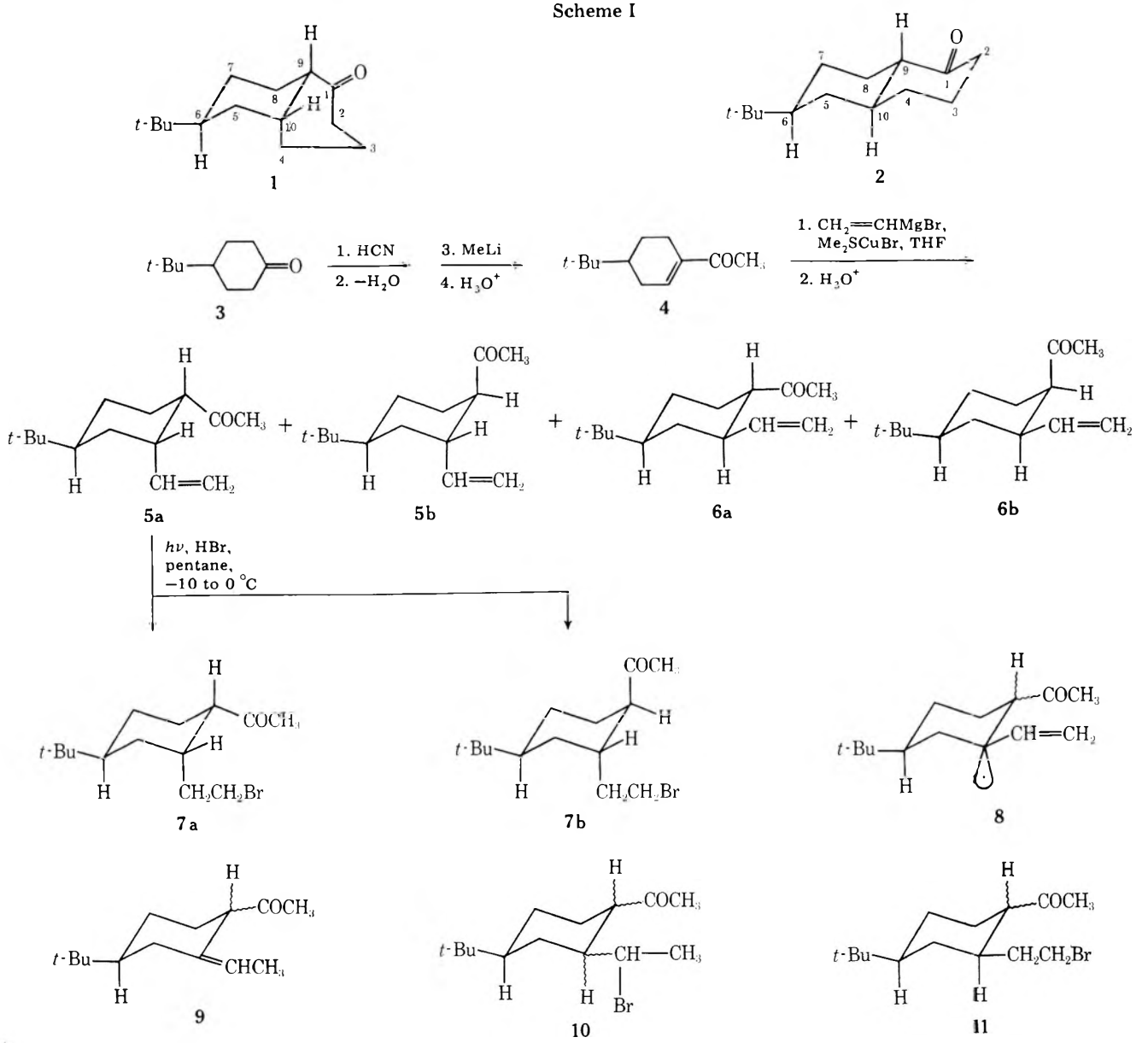
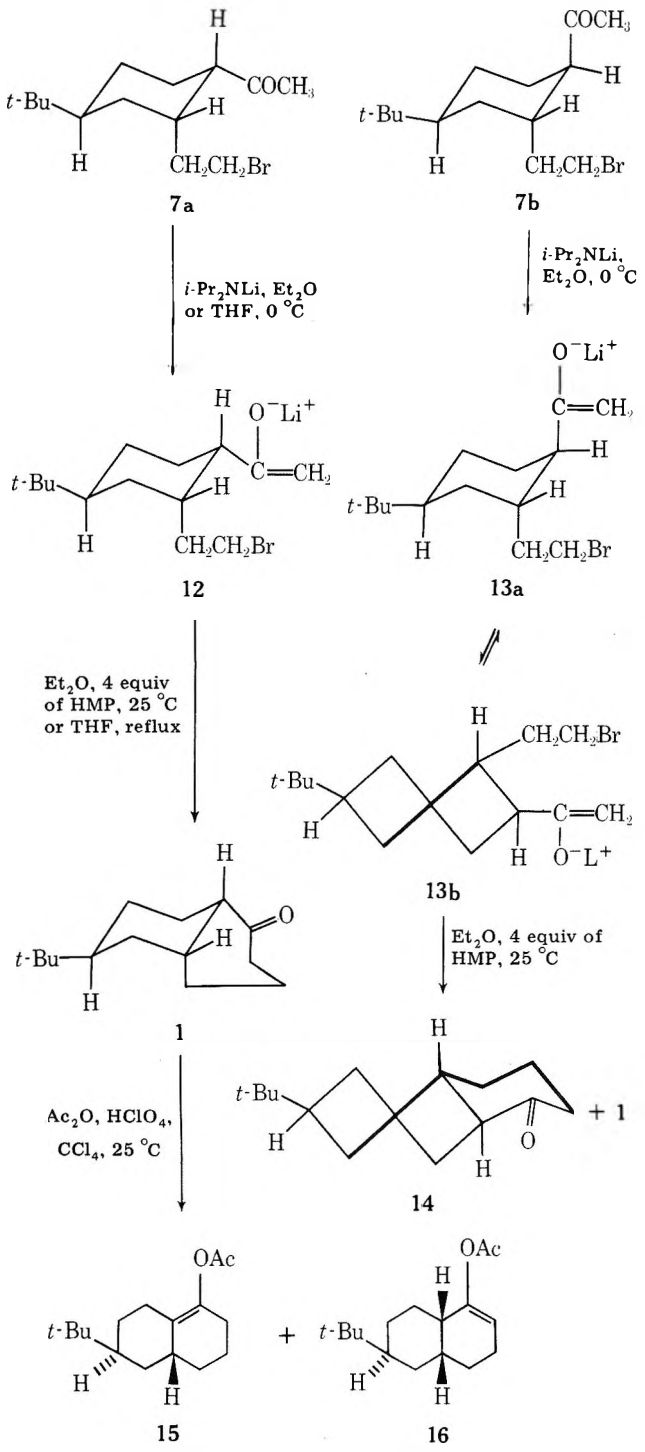
Scheme I



Since both epimers **5** have the appropriate stereochemical relationship between the *t*-Bu and CH_2=CH groups to be appropriate precursors for the desired decalone **1**, we examined the conversion of each epimeric olefin **5** to the corresponding bromo ketone **7** by the light-induced free-radical chain addition of HBr. In an earlier study[5a] of this HBr addition we noted a complication if this addition involved an olefin, $R_2CHCH{=}CH_2$, with a tertiary allylic CH bond. In such cases, including reactions with olefins **5** at 25 °C, the desired addition of a Br· radical to the double bond competes with abstraction of the allylic H atom by Br· to form an allylic radical such as **8**.[5a,6] Subsequent reaction of this allylic radical **8** with more HBr can either form a mixture of terminal olefins **5** and **6** or the structurally isomeric olefin **9**; free-radical chain addition of HBr to this olefin mixture **5**, **6**, and **9** then forms both the desired bromo ketones **7** and the unwanted isomers **10** and **11**. Thus, this competitive H-atom abstraction is clearly undesirable because it forms synthetic intermediates with either the wrong stereochemistry (**11**) or the wrong structure (**10**). Since free-radical addition reactions typically have a lower activation energy than free-radical atom abstraction reactions,[6,7] there was reason to expect that the importance of the competing H-atom abstraction reaction (to form **8**) could be diminished by lowering the reaction temperature.[6] In fact lowering the reaction temperature from 25 to 0 °C or less was sufficient to practically stop the competing reaction and allowed us to form a mixture of bromo ketones **7a** or **7b** from the vinyl ketone **5a** that was contaminated with <5% of the unwanted by-products **10** and **11**. Further purification by low-pressure liquid chromatography then allowed us to obtain pure samples of each desired bromo ketone epimer **7a** and **7b**.

Kinetic deprotonation of each of the bromo ketones **7a** and **7b** (Scheme II) with the hindered base *i*-Pr_2NLi as previously described[5b,c] allowed us to obtain the terminal enolates **12** and **13** needed for cyclization to the epimeric decalones **1** and **14**. Activation of the enolate **12**, either by addition of 4 molar equiv of $(Me_2N)_3PO$ (HMP) to an Et_2O solution at 25 °C[5b] or by refluxing a THF solution,[5c] resulted in cyclization to form the desired decalone **1** in 76–86% yield. This product was clearly different from the previously described[3] diastereoisomer **2**. Cyclization of the epimeric enolate **13** in refluxing THF yielded mainly the same decalone **1** indicating that the cyclization was accompanied by epimerization of the starting bromo ketone **7b** (→**7a**) and/or the initial product **14** (→**1**). However, when the cyclization was effected in Et_2O with 4 molar equiv of HMP, the major product was the trans-fused decalone **14** accompanied by lesser amounts of the cis-fused epimer **1**. Equilibration of these two decalone epimers with NaOMe in MeOH at 25 °C produced a mixture containing 6.5% **14** and 93.5% **1**. Thus, it is clear that the bromo enolate **13** is capable of cyclization, presumably via the twist boat

Scheme II



conformer **13b**, to form the trans-fused decalone **14**. If one considers the ΔG values for an axial CH_3CO group [1.17 kcal/mol,[8] a crude model for the enolate $C(OLi)=CH_2$] and an axial CH_3CH_2 group (1.75 kcal/mol,[8] a model for CH_2CH_2Br), the sum of these ΔG values (2.9 kcal/mol) is sufficiently close to the energy difference between chair and twist-boat cyclohexane rings (*ca.* 4 kcal/mol)[9] that appreciable concentrations of both conformers **13a** and **13b** would be expected. Thus, the successful cyclization **7b** → **14** is not an unreasonable result.

The usual[3] enol acetylation of the decalone **1** under equilibrating conditions (Ac_2O, $HClO_4$, CCl_4) produced a mixture of comparable amounts of enol acetates **15** and **16**. Since the stereoisomeric decalone **2** forms practically all more highly substituted enol acetate (analogous to **15**) under these same conditions, it seems likely that the octalin system represented by enol acetate **15** possesses a significant amount of conformational strain and may exist in a conformation with a twist-boat cyclohexane ring.[10] In any case, the methods described constitute an acceptable synthetic route to the decalone **1** and a suitable derivative **15** for the preparation of its lithium enolate. Our further studies of the alkylation stereochemistry of this enolate as well as the related question of the favored conformation of an enol derivative (e.g., **15**) are in progress and will be reported in a subsequent publication.

Experimental Section[11]

Separation of the Vinyl Ketones 5a and 5b. A 3.00-g sample of a crude product from reaction of the enone **4** with CH_2=$CHMgBr$ and Me_2SCuBr in THF[5a] [containing (GLC, silicone XE-60 on Chromosorb P) a derivative of the 1,2-adduct (retention time 5.2 min, ca. 6%), the ketone **6b** (14.0 min, ca. 0.3%), the ketone **5b** (18.3 min, ca. 34%), the ketone **6a** (20.6 min, ca. 5%), the enone **4** (22.6 min, ca. 3%), and the ketone **5a** (26.6 min, ca. 52%)] was chromatographed on a 2.5 × 100 cm column packed with Woelm silica gel (0.032–0.064 mm) and eluted with EtOAc–hexane (8:92 v/v). The early fractions contained 188 mg (6%) of liquid, $n^{25}D$ 1.4865, believed to be *p*-(*sec*-butyl)-*tert*-butylbenzene (formed from the 1,2-adduct by dehydration and C=C rearrangement). The spectral properties of the component were: IR (CCl_4), no OH or C=O absorption; NMR (CCl_4) δ 7.20 (2 H, d, J = 8 Hz, aryl CH), 7.00 (2 H, d, J = 8 Hz, aryl CH), 2.55 (1 H, sextet, J = 7 Hz, benzylic CH), 1.1–1.9 (11 H, m, aliphatic CH including a *t*-Bu singlet at 1.28), and 0.6–1.0 (6 H, m, two CH_3 groups); mass spectrum, *m/e* (rel intensity) 190 (M^+, 69), 176 (49), 175 (90), 173 (20), 162 (38), 161 (100), 146 (44), 131 (45), 91 (28), 57 (36), and 41 (19). Subsequent chromatographic fractions contained (GLC), in order of elution, 950 mg (32%) of relatively pure ketone **5b**, 288 mg (10%) of a mixture of ketones **5a** and **5b**, and 1.446 g (48%) of relatively pure ketone **5a**. Appropriate fractions were combined and rechromatographed to separate 798 mg (27%) of ketone **5b**, $n^{25}D$ 1.4730, that was further purified by short-path distillation to separate **5b** as a colorless liquid: mp 8.0–8.5 °C; $n^{25}D$ 1.4731; IR (CCl_4) 1712 (C=O), 1640 (C=C), and 921 cm^{-1} (CH=CH_2); mass spectrum, *m/e* (rel intensity) 208 (M^+, 0.7), 152 (40), 151 (17), 109 (62), 107 (16), 71 (19), 67 (17), 57 (81), 43 (100), and 41 (30); NMR (CCl_4) δ 4.8–6.3 (3 H, m, vinyl CH), 2.7–3.1 (1 H, m, allylic CH), 2.4–2.6 (1 H, m, COCH), 2.11 (3 H, s, $COCH_3$), 0.9–2.1 (7 H, m, aliphatic CH), and 0.81 (9 H, s, *t*-Bu). When the ^1H NMR spectrum of ketone **5b** was rerun at 100 mHz to examine the pattern attributable to the CHCO multiplet at δ 2.4–2.6, we obtained partial resolution into three closely spaced lines at 248, 250.5, and 253 Hz; the width at half-height of the envelope containing these peaks was 10 Hz. This observation is compatible with our assigned stereochemistry in which the COCH proton is equatorial and is coupled with two equatorial and one axial adjacent protons (typical J values all 2–3 Hz).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.90; H, 11.74.

Appropriate later fractions that were combined and rechromatographed afforded 1.17 g (39%) of pure (GLC) ketone **5a**, mp 24–25 °C, $n^{25}D$ 1.4728 (lit. $n^{25}D$ 1.4728,[4b] mp 17.5–18 °C[5a]), that was identified with a previously described[4b] sample by comparison of IR, NMR, and mass spectra.

Separation of the Vinyl Ketones 6a and 6b. Fractions from several reactions containing (GLC, silicone XE-60 on Chromosorb P) primarily the ketones **6b** (retention time 10.2 min) and **6a** (15.4 min) were combined and separated by preparative liquid chromatography on a column packed with silica gel and eluted with EtOAc–hexane (6:94 v/v). The early fractions contained (GLC) the ketone **6b** separated as a colorless liquid: IR (CCl_4) 1715 cm^{-1} (C=O); NMR (CCl_4) δ 5.6–6.2 (1 H, vinyl CH), 4.7–5.2 (2 H, m, vinyl CH), 2.77 (1 H, m, allylic CH), 1.0–2.3 (11 H, m, aliphatic CH including a CH_3CO singlet at 2.02), and 0.85 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 208 (M^+, 0.5), 152 (13), 109 (26), 71 (23), 58 (100), 57 (50), 43 (69), 42 (18), 41 (24), and 39 (14).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.81; H, 11.67.

Later chromatographic fractions contained (GLC) the ketone **6a** separated as a colorless liquid: IR (CCl_4) 1715 cm^{-1} (C=O); NMR (CCl_4) δ 4.8–6.1 (3 H, m, vinyl CH), and 0.8–2.6 (21 H, m, aliphatic CH including a CH_3CO singlet at 1.99 and a *t*-Bu singlet at 0.89); mass spectrum, *m/e* (rel intensity) 208 (M^+, 4), 151 (23), 109 (36), 107 (17), 67 (18), 57 (88), 43 (100), and 41 (32).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.74; H, 11.65.

The two ketones **6** were equilibrated to establish which epimer was more stable corresponding to the isomer **6a** with an equatorial acetyl

group. A solution of 21 mg of ketone **6b** and 21 mg of n-$C_{19}H_{40}$ (an internal standard) in 1 mL of MeOH and 1 mL of THF was treated with 5.5 μL (0.2 equiv) of methanolic 3.6 M NaOMe and stirred at 25.0 °C. Periodically aliquots of the solution were removed, quenched in an aqueous phosphate buffer (pH 7.0), extracted with hexane, dried, and analyzed (GLC, apparatus calibrated with known mixtures). An additional portion (0.3 equiv) of methanolic 3.6 M NaOMe was added after 5 h. After 140 h at 25 °C, the solution contained 1.3% of ketone **6b** and 98.7% of ketone **6a** (93% recovery of **6**). From a comparable experiment starting with the ketone **6a**, after 140 h at 25 °C the solution contained >98% of the ketone **6a** and <2% of the ketone **6b** (100% recovery of **6**).

Preparation of the Bromo Ketones 7. The previously described[5a] apparatus and reaction procedures were followed except that the photochemical reactor was cooled by circulating cold MeOH from an external, thermostated cooling system. The temperature of the circulating MeOH was monitored and kept at 0 to −1 °C at the outlet from the cooling jacket of the photochemical apparatus. In a typical experiment, a cold (0 °C or less) solution of 1.90 g (9.13 mmol) of unsaturated ketone **5a** in 350 mL of pentane was irradiated with ultraviolet light for 12 min while a stream of anhydrous HBr was passed through the solution. Then the solution was purged with N_2 (to remove excess HBr), washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 2.25 g (85%) of crude bromo ketone **7** product as a colorless liquid that contained (NMR analysis) ca. 35% of **7b** and ca. 65% of **7a** but none of the secondary bromide **10** was detected. A 1.00-g aliquot of the product was chromatographed on Woelm silica gel with an EtOAc–hexane eluent (6:94 v/v) to separate 105 mg of earlier fractions containing (NMR analyses) the bromo ketone **7b** followed by 453 mg of fractions containing various mixtures of **7a** and **7b.** Subsequent fractions contained 410 mg of the bromo ketone **7a.** The intermediate fractions were rechromatographed on silica gel to separate 228 mg of **7b** (total yield 333 mg or 28%) and 208 mg of **7a** (total yield 618 mg or 53%). In another comparable hydrobromination of 1.50 g of the vinyl ketone **5a** for 10 min at −1 to 0 °C, chromatography separated 90 mg (ca. 4%) of early fractions containing (NMR) mixtures of dibrominated products and secondary bromide **10** followed by 1.74 g (84%) of fractions containing bromo ketones **7a** (ca. 65% of the mixture) and **7b** (ca. 35% of the mixture).

The ketone **7a** was obtained as a colorless liquid: n^{25}_D 1.4969; IR (CCl_4) 1710 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 3.15–3.5 (2 H, m, CH_2Br), 2.2–2.5 (1 H, m, CHCO), 1.0–2.1 (13 H, m, aliphatic CH including a CH_3CO singlet at 2.08), and 0.87 (9 H, s, t-Bu); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 209.8 (s), 54.3 (d), 40.8 (d), 33.7 (d), 32.1 (s), 31.9 (t), 29.8 (t), 29.3 (t), 28.3 (t), 27.3 (q, 3 C atoms), 26.2 (q), and 22.4 (t); mass spectrum, m/e (rel intensity) 290 (M^+, 0.05), 288 (M^+, 0.05), 208 (15), 193 (21), 151 (21), 123 (35), 110 (12), 109 (19), 95 (10), 81 (12), 57 (48), 43 (100), and 41 (27).

The ketone **7b** was obtained as a colorless liquid: n^{25}_D 1.4968; IR (CCl_4) 1710 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 3.37 (2 H, t, J = 7 Hz, CH_2Br), 1.0–2.6 (14 H, m, aliphatic CH including a CH_3CO singlet at 2.10), and 0.82 (9 H, s, t-Bu); mass spectrum, m/e (rel intensity) 290 (M^+, 0.5), 288 (M^+, 0.5), 209 (11), 153 (12), 123 (10), 109 (18), 95 (10), 81 (11), 71 (23), 57 (71), 55 (12), 43 (100), and 41 (29).

The most satisfactory analytical method for mixtures of the epimeric bromo ketones **7** utilized the ^1H NMR spectra. The ketone **7a** exhibited a t-Bu singlet at δ 0.87 with a complex multiplet (CH_2Br) centered at δ 3.33 while the ketone **7b** exhibited a t-Bu singlet at a higher field (δ 0.82) with a triplet (CH_2Br) at δ 3.37. The presence of the secondary bromide **10** in this mixture is readily detected by the presence of a t-Bu singlet at δ 0.89 and, especially, a CHBr multiplet at δ 4.22. When samples of either pure bromo ketone **7a** or **7b** (from chromatography) were distilled in a short path still (ca. 104 °C at 0.01 mm), mixtures of the two epimers were obtained. Thus, distillation of pure ketone **7a** afforded a colorless liquid, n^{25}_D 1.4970, that contained (NMR analysis) ca. 65% **7a** and ca. 35% **7b.**

Anal. Calcd for $C_{14}H_{25}BrO$: C, 58.12; H, 8.73; Br, 27.62. Found: C, 58.20; H, 8.72; Br, 27.49.

When an 835-mg sample of the epimeric vinyl ketone **5b** in 300 mL of pentane was subjected to the photoinitiated addition of HBr for 6 min at 25 °C, the resulting crude bromo ketone product amounted to 1.076 g. Chromatography on silica gel with an EtOAc–hexane eluent (8:92 v/v) separated in earlier fractions 44 mg of an unidentified crude dibrominated product as a colorless solid, mp 104.5–105.5 °C, followed by 18 mg (1.5%) of the crude secondary bromide **10** as a colorless liquid: NMR (CCl_4) δ 4.22 (1 H, q of d, J = 7 and 2 Hz, CHBr) and 0.8–2.4 [24 H, m, aliphatic CH including a CH_3CO singlet at 2.15, a CH_3 doublet (J = 7 Hz) at 1.65, and a t-Bu singlet at 0.89]. Later fractions contained 877 mg (76%) of mixtures of bromo ketones **7a** (ca. 64%) and **7b** (ca. 36%). The similar hydrobromination of 242 mg of vinyl ketone **5a** in 300 mL of pentane at 25 °C for 5 min afforded, after chromatography, 114 mg (ca. 32%) of a mixture of dibromo product and secondary bromo ketone **10** and 141 mg (42%) of fractions containing mixtures of bromo ketones **7a** and **7b.** Thus, it appears that the H-atom abstraction leading to by-products **10** and **11** is more serious at 25 °C with the vinyl ketone **5a** than with its epimer **5b.** The photoinitiated addition of HBr was repeated with a solution of 140.5 mg of the vinyl ketone **5b** in 310 mL of pentane at 0 °C for 6.5 min. After the crude product (183.6 mg) had been chromatographed, the fractions were subjected to the above NMR analysis. From the fraction weights and NMR analysis, the yields were estimated to be 28% bromo ketone **7b,** 52% bromo ketone **7a,** 3% secondary bromide **10,** and 3% dibrominated product.

Cyclization of Bromo Ketone 7a. A. In Et_2O Solution. Following a previously described[5b] procedure, a solution of 386 mg (1.33 mmol) of the bromo ketone **7a** in 10 mL of Et_2O was added, dropwise and with stirring during 30 min, to a cold (−78 °C) solution of 1.40 mmol of i-Pr_2NLi and 2 mg of 2,2′-bipyridyl (an indicator) in 2.7 mL of a pentane–hexane mixture and 20.6 mL of Et_2O. After the resulting solution of the enolate **12** (0.04 M) had been warmed to 0 °C, 1.00 g (5.58 mmol, 4 molar equiv per Li^+) of HMP was added and the solution was stirred at 0–2 °C for 20 min, allowed to warm to 23 °C during 20 min, and stirred at 23 °C for 40 min. The reaction mixture was partitioned between Et_2O and aqueous $NaHCO_3$ and the organic phase was dried and concentrated to leave 317 mg of crude product as a yellow liquid. An aliquot of the crude product was mixed with a known weight of n-$C_{20}H_{42}$ (an internal standard) for GLC analyses (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures); the crude product contained several minor unidentified impurities (retention times 5.2, 6.9, 9.4, and 14.8 min), n-$C_{20}H_{42}$ (28.0 min), the $trans$-decalone **14** (34.6 min, 2.4% yield), and the cis-decalone **1** (41.5 min, 86% yield). A 275-mg aliquot of the crude product was chromatographed on Woelm silica gel with an EtOAc–hexane eluent (8:92 v/v) to separate 8.5 mg (3.5%) of an early fraction containing (NMR) the unchanged bromo ketone **7a** accompanied by small amounts of ketones **1** and **14.** Later fractions contained 184 mg (76%) of ketone **1** that was identified with the subsequently described sample by comparison of IR and NMR spectra and GLC retention times and shown to differ from the previously described[3] decalone diastereoisomer **2** by comparison of IR spectra.

B. In THF Solution. To a cold (−70 °C) solution of 8.11 mmol of i-Pr_2NLi and 4 mg of 2,2′-bipyridyl (an indicator) in 14.2 mL of a pentane–hexane mixture and 120 mL of THF was added, dropwise and with stirring during 45 min, a solution of 2.233 g (7.73 mmol) of the bromo ketone **7a** in 25 mL of THF. The resulting orange solution of the enolate **12** (0.05 M) was warmed to −20 °C during 10 min and then immersed in a preheated bath and refluxed for 45 min. After the reaction mixture had been subjected to the previously described isolation procedure, the crude product amounted to 1.60 g of red liquid. After an aliquot of the crude product had been mixed with n-$C_{20}H_{42}$, GLC analysis indicated the presence of ketone **1** (78% yield) and ketone **14** (9% yield). Distillation of the crude product separated 1.29 g (80%) of a mixture of ketones **1** (90% of mixture) and **14** (10% of mixture), bp 115–117 °C (0.35 mm), n^{25}_D 1.4365–1.4868, and left 0.22 g of a brown higher molecular weight residue. A 1.11-g aliquot of the distillate was chromatographed on Woelm silica gel to separate 83 mg (6%) of the $trans$-decalone **14** and 884 mg (64%) of the cis-decalone **1.** These latter fractions were distilled to separate 820 mg of the pure cis-decalone **1** as a colorless liquid: bp 81–82 °C (0.08 mm); n^{25}_D 1.4859; IR (CCl_4) 1709 cm^{-1} (C=O); UV_{max} (95% EtOH) 299 nm (ε 18); ^1H NMR (CCl_4) δ 0.9–2.4 (15 H, m, aliphatic CH) and 0.86 (9 H, s, t-Bu); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 214.5 (s), 53.1 (d), 41.2 (d), 37.5 (d and t, 2 C atoms), 32.0 (s), 31.4 (t), 27.2 (q, 3 C atoms), 26.8 (t), 25.8 (t), 25.7 (t), and 25.2 (t); mass spectrum, m/e (rel intensity) 208 (M^+, 13), 151 (22), 133 (30), 112 (22), 110 (34), 97 (98), 91 (32), 84 (28), 67 (34), 57 (100), 55 (25), and 41 (64).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.64.

A collected (GLC) sample of the $trans$-decalone **14** was distilled in a short-path still to separate the ketone **14** as a colorless liquid: n^{25}_D 1.4853; IR (CCl_4) 1710 cm^{-1} (C=O, spectrum clearly different from the IR spectra of decalones **1** and **2**); NMR (CCl_4) δ 1.0–2.4 (15 H, m, aliphatic CH) and 0.90 [9 H, s, t-Bu (this signal is at 0.04 ppm lower field than the t-Bu signal at 0.86 for the cis-decalone **1**)]; mass spectrum, m/e (rel intensity) 208 (M^+, 12), 152 (24), 123 (20), 110 (35), 97 (21), 67 (22), 57 (100), 55 (24), 44 (24), and 41 (64).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found C, 80.89; H, 11.73.

In a larger scale preparation, 6.22 g (29.9 mmol) of a mixture of vinyl

ketones **5a** and **5b** (isolated by liquid chromatography) was subjected to light-catalyzed hydrobromination at 0 °C to yield, after column chromatography, 7.05 g (24.4 mmol, 82%) of a mixture of epimeric bromo ketones **7a** and **7b**. After a solution of this mixture in 30 mL of THF has been added to a cold (−78 °C) mixture of 400 mL of THF and 52.2 mL of a hexane–pentane solution containing 25.6 mmol of $(i\text{-Pr})_2$NLi, the resulting solution was refluxed for 75 min and then subjected to the usual isolation procedure. Chromatography of the crude product on silica gel separated 4.13 g (82% based on the bromo ketones **7** or 66% overall) of a mixture of decalones **1** and **14**.

Cyclization of the Bromo Ketone 7b. A. In Et_2O Solution. A solution of the enolate **13** (0.05 M) was prepared by the slow (40 min) addition of a solution of 475 mg (1.64 mmol) of the bromo ketone **7b** in 4 mL of Et_2O to a cold (−70 °C) solution of 1.73 mmol of $i\text{-Pr}_2$NLi and 2–3 mg of 2,2′-bipyridyl in 3.2 mL of a pentane–hexane mixture and 25 mL of Et_2O. After the orange enolate solution had been warmed to 0 °C, 1.24 g (6.92 mmol, 4 molar equiv per Li^+) of HMP was added and the mixture was stirred at 0–2 °C for 20 min, at 2–22 °C for 20 min, and the reflux (33 °C) for 20 min. After the reaction mixture had been partitioned between aqueous $NaHCO_3$ and Et_2O, the organic phase was dried, concentrated, taken up in pentane, washed with several portions of aqueous NaCl (to remove residual HMP), and again dried and concentrated. The residual red liquid (328 mg) contained (IR and NMR analysis) a mixture of the starting bromo ketone **7b** (no **7a** was detected) and the epimeric decalones **1** and **14**. Analysis by GLC (silicone XE-60 on Chromosorb P) indicated the presence of several relatively rapidly eluted components (retention times 6.5, 9.9, and 16.3 min) believed to be various enol ether isomers from decomposition of the bromo ketone **7b** in the GLC apparatus, the *trans*-decalone **14** (33.4 min, 17% of the decalone product), and the *cis*-discalone **1** (38.0 min, 83% of the decalone product). From a second comparable reaction (reaction time 20 min at 0–2 °C, 20 min at 0–25 °C, and 40 min at 25 °C) where an aliquot of the crude product was mixed with a weighed amount of $n\text{-}C_{20}H_{42}$, the calculated yield (GLC) was 44% of *cis*-decalone **1** and 12% of *trans*-decalone **14**.

A 205-mg aliquot of the crude product was chromatographed on Woelm silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 92 mg (45%) of early fractions containing (NMR analysis) the bromo ketone **7b** (ca. 58% of the mixture) and the *trans*-decalone **14** (ca. 42% of the mixture) and 22 mg (11%) of later fractions containing (NMR analysis) the bromo ketone **7a** (ca. 10% of the mixture) and the *cis*-decalone **1** (ca. 90% of the mixture). In addition, 48 mg of fractions containing various minor unidentified components and 33 mg (ca. 16%) of slowly eluted fractions containing higher molecular weight materials (presumably from intermolecular alkylation) were isolated. Based on fraction weights and NMR analysis, the calculated yields were 26% recovery of the bromo ketone **7b**, 1% of the bromo ketone **7a**, 19% of the *trans*-decalone **14**, and 10% of the *cis*-decalone **1**. Collected (GLC) samples of the *cis*-decalone **1** and the *trans*-decalone **14** were identified with previously described samples by comparison of IR spectra and GLC retention times.

B. In THF Solution. A solution of the enolate **13** (0.05 M) was obtained by the slow (15 min) addition of a solution of 310 mg (1.07 mmol) of the bromo ketone **7b** in 2.0 mL of THF to a cold (−60 °C) solution of 1.13 mmol of $i\text{-Pr}_2$NLi and 2 mg of 2,2′-bipyridyl in 2.1 mL of a pentane–hexane mixture and 16.8 mL of THF. The resulting yellow solution was stirred at −60 °C for 5 min and then immersed in a preheated bath and refluxed for 2 h. After the reaction mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried and concentrated to leave 182 mg of crude red liquid product. A 175-mg aliquot was chromatographed on Woelm silica gel with an Et_2O–hexane eluent (9:91 v/v) to separate 4 mg of unidentified rapidly eluted material followed by 35 mg (16% yield) of the *trans*-decalone **14**, 95 mg (44% yield) of the *cis*-decalone **1**, and 37 mg (ca. 17% yield) of a mixture of higher molecular materials. Collected (GLC) samples of the decalones **1** and **14** were identified with previously described samples by comparison of IR spectra and GLC retention time.

Equilibration of Decalones 1 and 14. A solution of 31.2 mg (0.15 mmol) of the *trans*-decalone **14**, 15.4 mg of $n\text{-}C_{19}H_{40}$, and 0.03 mmol of NaOMe in 1.5 mL of MeOH and 1.5 mL of Et_2O was maintained at 25.0 °C. Aliquots (0.3 mL) were removed, diluted with 0.3 mL of Et_2O, and partitioned between hexane and an aqueous buffer (pH 7) at the following time intervals: 0.5, 8, 10, 13, and 31 h. The hexane phases were concentrated and analyzed by GLC (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures); the retention times of the components were: $n\text{-}C_{19}H_{40}$, 16.0 min; *trans*-decalone **14**, 31.1 min; *cis*-decalone **1**, 36.3 min. The recovery of ketones **1** and **14** in the various aliquots ranged from 96 to 100% and the composition of the mixture became constant after 10 h at 6.5% *trans*-ketone **14** and 93.5% *cis*-ketone **1**. Comparable mixtures of **1** and **14** were obtained when the *cis*-ketone **1** was subjected to the same equilibrating conditions.

Preparation of the Enol Acetates 15 and 16. A solution of 312 mg (1.5 mmol) of the ketone **1** and 811 mg (7.9 mmol) of Ac_2O in 4.5 mL CCl_4 was treated with 0.025 mL of aqueous 70% $HClO_4$ and the resulting mixture was allowed to stand at 25 °C for 20 min. After the reaction mixture had been neutralized with aqueous $NaHCO_3$, it was partitioned between aqueous $NaHCO_3$ and an Et_2O–hexane mixture. The organic layer was dried, concentrated, and distilled at 1.0 mm in a short-path still to separate 330 mg (88%) of a mixture of enol acetates **15** and **16** as a pale yellow liquid. This material contained (GLC, silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) 54% of the enol acetate **16** (retention time 51.8 min) and 46% of the enol acetate **15** (39.4 min) accompanied by less than 5% of the starting ketone **1** (44.2 min). This product was chromatographed on silica gel with an EtOAc–hexane eluent to separate early fractions containing 109 mg (29%) of the enol acetate **15** as a colorless liquid: n^{25}_D 1.4855; IR (CCl_4) 1752 (enol ester C=O) and 1704 cm^{-1} (weak, C=C); NMR (CCl_4) δ 1.0–2.4 (17 H, m, aliphatic CH including a CH_3CO singlet at 2.03) and 0.84 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 250 (M^+, 5), 208 (100), 151 (75), 149 (20), 133 (37), 123 (72), 110 (51), 91 (23), 57 (50), 55 (24), 43 (44), and 41 (39).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47; mol wt, 250.1933. Found: C,77.02; H, 10.72; mol wt. 250.1917.

Later chromatographic fractions contained 132 mg (35%) of the enol acetate **16** as a colorless liquid: n^{25}_D 1.4837; IR (CCl_4) 1758 (enol ester C=O) and 1690 cm^{-1} (C=C); NMR (CCl_4) δ 5.1–5.3 (1 H, m, vinyl CH), 1.0–2.5 (16 H, m, aliphatic CH including a CH_3CO singlet at 2.03), and 0.83 (9 H, s, *t*-Bu); mass spectrum, *m/e* (rel intensity) 250 (M^+, 6), 208 (96), 190 (26), 175 (20), 152 (29), 151 (83), 150 (27), 149 (26), 134 (64), 133 (100), 132 (22), 123 (24), 112 (24), 110 (29), 97 (90), 91 (61), 84 (53), 81 (23), 67 (36), 57 (85), 55 (40), 43 (72), and 41 (54).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47; mol wt, 250.1933. Found: C, 77.06; H, 10.70; mol wt, 250.1897.

Subsequent fractions from the chromatography contained 13.6 mg (4%) of the starting ketone **1**. In order to establish the presence of the cis-ring fusion in the enol acetate **16**, a solution of 39.6 g (0.16 mmol) of the enol acetate **16** and 0.9 mL of aqueous 1 M HCl in 2.4 mL of THF was stirred at 25 °C for 72 h. Aliquots of the solution were removed periodically and partitioned between Et_2O and aqueous $NaHCO_3$. Each organic layer was mixed with a known weight of $n\text{-}C_{19}H_{40}$ (an internal standard) for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The retention times for the various components were: $n\text{-}C_{19}H_{40}$, 22.9 min; enol acetate **15** and trans-fused ketone **14**, 37.9 min (not resolved); cis-fused ketone **1**, 47.8 min; enol acetate **16**, 55.2 min. As the hydrolysis proceeded the enol acetate **16** was slowly converted to the *cis*-ketone **1** accompanied by little if any (4% or less) of the *trans*-ketone **14** and the enol acetate **15**. After 72 h approximately 60% of the enol acetate **16** had been converted to the *cis*-ketone **1**. Collected (GLC) samples of these two products were identified with authentic samples by comparison of IR spectra and GLC retention times.

Registry No.—**1**, 67238-07-7; **4**, 37881-09-7; **5a**, 54678-11-4; **5b**, 54678-12-5; **6a**, 54678-13-6; **6b**, 54678-14-7; **7a**, 61675-07-8; **7b**, 61675-06-7; **10**, 61675-09-0; **12**, 67238-08-8; **13**, 67238-09-9; **14**, 67238-10-2; **15**, 67238-11-3; **16**, 67238-12-4; vinyl bromide, 593-60-2; *p*-(*sec*-butyl)-*tert*-butylbenzene, 25027-33-2.

References and Notes

(1) This research has been supported by Public Health Service Grant RO1-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.
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(11) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The ^1H NMR spectra were determined at 60 mHz with a Varian, Model T-60-A, NMR spectrometer and the ^{13}C NMR spectra were determined at 25 mHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer, Model RMU-7, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

Acid Catalysis of the Claisen Rearrangement. 2. Formation of the Benzofurobenzopyran and Benzofuro[3,2-*b*]benzofuran Skeletons from 1,4-Bis(aryloxy)-2-butynes

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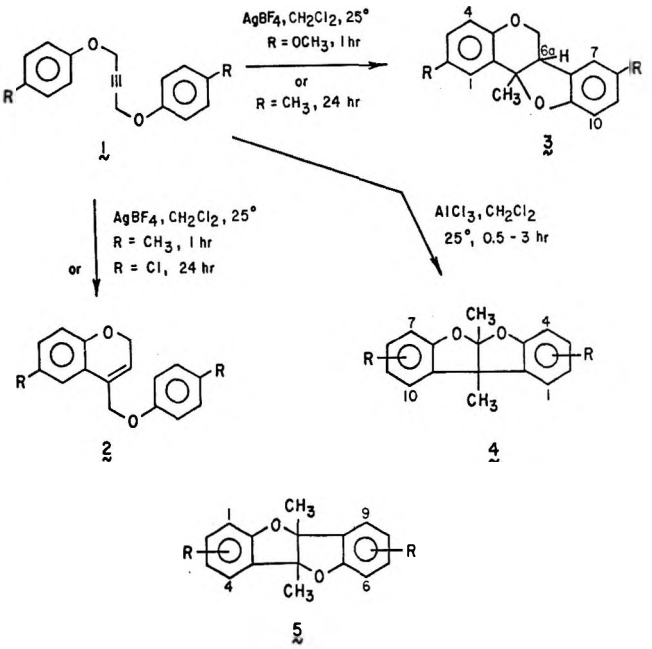
1,4-Bis(aryloxy)-2-butynes (**1**) can be selectively converted into 4-(aryloxymethyl)-2*H*-chromenes (**2**), 6*H*-benzofuro[3,2-*c*]-6a,11a-dihydro-11a-methylbenzopyrans (**3**), or 5a,10b-dihydro-5a,10b-dimethylbenzofuro[2,3-*b*]benzofurans (**4**) by treating a dichloromethane solution of **1** with mercuric trifluoroacetate, silver tetrafluoroborate, or anhydrous aluminum chloride, respectively. A mechanism involving charge-induced Claisen rearrangement triggered by π complex formation between the heavy metal ion and the C–C multiple bond (in **1** and **2**) is postulated for formation of **2** and **3**. Sequential charge-induced Claisen rearrangement of **1** into **3** by coordination of $AlCl_3$ with the oxygen atoms of **1** and **2** followed by ionic rearrangement of **3** into **4** is also postulated. The differing efficacy of metal ions in promoting isomerization of **1**, **2**, and **3** is discussed.

In a synthetic program designed to provide modified pterocarpin compounds related to pisatin, a phytoalexin isolated from stressed peas, *Pisum sativum* L., we required a covenient procedure for obtaining 6*H*-benzofuro[3,2-*c*]-6a,11a-dihydro-11a-methylbenzopyran derivatives (**3**). The reported[1] synthesis of such compounds involves Claisen rearrangement of 1,4-bis(aryloxy)-2-butynes. This procedure requires high temperatures (>200 °C) and long reaction times (~12 h).

Schmid[2] in a series of papers has reported that charge-induced Claisen rearrangements can be conducted at substantially lower temperatures and may show rate increases relative to the thermal process of up to 10^{10}. Two basic approaches to charge-induced Claisen rearrangements applicable to the case at hand have been described: (a) charge formation by heteroatom complexation with a hard[3] Lewis acid, e.g., BCl_3,[2] $ZnCl_2$,[4] H^+;[5] or (b) charge formation by coordination to C–C multiple bonds by soft Lewis acids, e.g., Ag^+,[6] Hg^{2+}.[7]

We therefore undertook a study of the reaction of 1,4-bis(aryloxy)-2-butynes with various hard and soft Lewis acids and now wish to report: (1) a very simple procedure for obtaining oxygen-substituted compounds **3** using silver tetrafluoroborate; and (2) a novel rearrangement of 1,4-bis(aryloxy)-2-butynes and isomers to 5a,10b-dihydro-5a,10b-dimethylbenzofuro[2,3-*b*]benzofurans (**4**) using anhydrous aluminum chloride (Scheme I).

Scheme I



Results

The conversion of phenyl propargyl ether into 2*H*-chromene by means of $AgBF_4$ in refluxing chloroform has been reported.[6] In attempts to extend this procedure to 1,4-bis-(aryloxy)-2-butynes (**1**) we have found that the product obtained is a function of both the aryl group and the reaction time. The data are summarized in Table I. With activated aromatic rings **1** rearranges within 1 h into **3**. Less activated compounds undergo rearrangement more slowly. Thus, **1d** gives the 2*H*-chromene **2d** while **1e** remains unchanged after 1 h at room temperature. After 24 h, however, **1d** gives **3d** and **1e** gives the 2*H*-chromene **2e**. For moderately activated compounds, i.e., **1b–d**, this is the method of choice for synthesis of **3**.[8]

Silver trifluoroacetate is also an effective catalyst. Mercuric trifluoroacetate was less effective, rearranging only **1b** into the corresponding 2*H*-chromene. Aryl 2-propynyl ethers tolerate a broader range of substituents in the generation of 2*H*-chromene derivatives upon treatment with mercuric trifluoroacetate.[7b] Thallium trifluoroacetate was not a catalyst.

Examination of hard Lewis acids[9] revealed yet another

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Table I. Effect of Time and Substituent on the Rearrangement of 1 Catalyzed by $AgBF_4$[a]

	R (in 1)	registry no.	reaction time, h	product (% yield)	registry no.
a	2-OMe	4200-25-3	1	no reaction	
			24	no reaction	
b	4-OMe	4200-28-6	1	**3** (72)	41229-98-5
			24	**3** (61)	
c	3,4-OCH_2O	67238-29-3	1	**2** (59)	
d	4-Me	4200-18-4	1	**2** (55)	37113-57-8
			24	**3** (87)	14298-17-0
e	4-Cl	4200-26-4	1	no reaction	37104-73-7
			24	**2** (69)	

[a] Compound **1a** was very unreactive in all catalyst systems, being recovered unchanged after prolonged treatment with $Hg(O_2CCF_3)_2$ and only very slowly converted into **4** with $AlCl_3$. The predominant pathway was ether cleavage in the former reaction.

selective reorganization. Thus, treatment of a series of **1** with anhydrous $AlCl_3$ gave **4** in good to excellent yield (Table II).

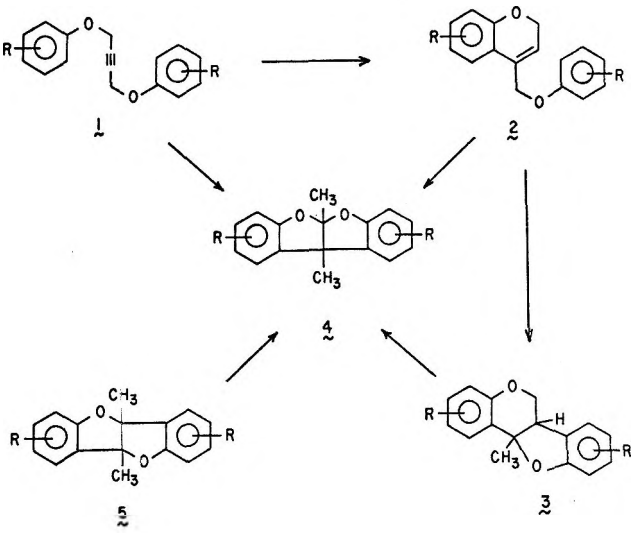
The assignment of structure **4** to these products rests on spectroscopic data and comparison of spectroscopic and physical data for **4b** and **4d** with data appearing in the literature.[11] We also assign the cis configuration to these compounds, as Dreiding models indicate the trans isomer is extremely strained.

In attempting to obtain more information about the **1** → **4** conversion we subjected various isomers of **1**, which we felt might be intermediates in the formation of **4**, to aluminum chloride in CH_2Cl_2. In all cases these isomers rearranged smoothly to **4**. Thus, treatment of **2g** and **3g** with $AlCl_3$ gave **4g** in 60 and 67% yield, respectively. Additionally, we prepared 4b,9b-dihydro-4b,9b-dimethyl-1,6-dichlorobenzofuro[3,2-*b*]benzofuran[12] (**5g**) and found that it also rearranges to **4** in the presence of $AlCl_3$ (although at a slower rate than **2** or **3**). The results are summarized in Scheme II.

Discussion

Transformation of **1** into **2** in the presence of HgO (acetic acid, 100 °C) has been reported[10] and attributed to acid-catalyzed cyclization of 1,4-diphenoxy-2-butanone (**6**) resulting from hydration of **1**. We have prepared several derivatives of

Scheme II



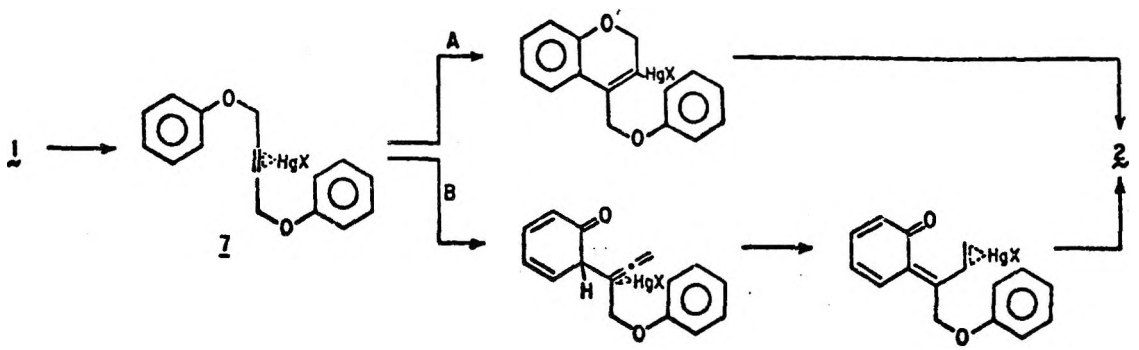
6 and find that none produce **2** when subjected to the cyclization conditions (either glacial acetic acid/HgO/100 °C or $CH_2Cl_2/Hg(O_2CCF_3)_2$/25 °C). An additional mechanism involving concerted sigmatropic rearrangement triggered by the charge induced by π-complex formation[13] can also be postulated (path B, Scheme III). Another possibility involving a σ complex, cyclization of this ion, and protonolysis of the C–Hg bond[14] (path A, Scheme III) produces a "two-step" sigmatropic mechanism[7a] which may be viewed as a metal ion catalyzed Friedel–Crafts alkenylation of an aromatic ring by an alkyne.[15,16] Path B represents a concerted sigmatropic process, paralleling that proposed by Schmid;[6] a large body of evidence for silver ion catalyzed sigmatropic rearrangement of phenyl propynyl ether has been published[6] and we have accumulated some related preliminary evidence pertaining to the sigmatropic nature of the mercuric ion catalyzed counterpart. Full discussion of this data will be deferred to a subsequent report. Two indirect points may be advanced at this time to discredit path A. First of all, two σ complexes may form from **7**, resulting in either a five- or a six-membered ring-containing product depending on the site of localization of the (+) charge. We have never observed any benzofuranoid compounds in the crude reaction mixture even though they were sought. Additionally, 1-phenyl-4-(*p*-bromophenoxy)-1-butyne, which could cyclize to a dihydrobenzoxepin via a Friedel–Crafts type reaction, does not produce any dihydrobenzoxepin, but instead produces only 1-phenyl-4-(*p*-bromophenoxy)-1-butanone under a variety of reaction conditions (see Experimental Section). These findings point to the uniqueness of 2*H*-

Table II. Data for 5a,10b-Dihydro-5a,10b-dimethylbenzofuro[2,3-*b*]benzofurans (4)[a]

	R (in 1)	registry no.	yield, %	registry no. (4)	mp, °C	NMR (5a and 10b methyls only)
b	4-OMe[b]		74	67238-32-8	122–123[c]	1.72 (3 H, s), 1.63 (3 H, s)
d	4-Me		77	67238-33-9	195–196[d]	1.73 (3 H, s), 1.60 (3 H, s)
e	4-Cl		63	67238-34-0	187.5–189.5	1.77 (3 H, s), 1.67 (3 H, s)
f	4-NO_2,[e] 3-CF_3	67238-30-6				
g	2-Cl	4467-00-9	30[f]	67238-35-1	223–224	1.83 (3 H, s), 1.68 (3 H, s)
h	2,4-Cl_2	37104-62-4	27	67238-36-2	267–269	1.85 (3 H, s), 1.68 (3 H, s)
i	2-F	67238-31-7	30[g]	67238-37-3	179.5–180.5	1.85 (3 H, s), 1.72 (3 H, s)

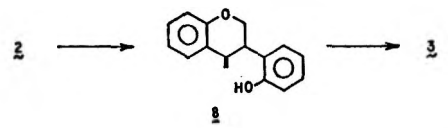
[a] In all cases examined the predominant mode of mass spectral fragmentation involves loss of methyl radical. Satisfactory analytical data were reported for all compounds. [b] In one run 10 mol % $AlCl_3$ was used, giving an 88% yield of **4b**. For less activated compounds this quantity of $AlCl_3$ gave a sluggish reaction. Yields in all reactions in this paper are not optimized. [c] Lit. mp 116 °C; NMR (methyl H's) δ 1.65 (3 H, s), 1.60 (3 H, s) [ref 11]. [d] Lit. mp 196–197 °C [K. Sisido, H. Nozaki, and T. Ilwako, *J. Am. Chem. Soc.*, **71**, 2037 (1949)]; 201–202 °C; NMR (methyl H's) δ 1.73 (3 H, s), 1.63 (3 H, s) [ref 11]. [e] Starting material recovered (80% recovery). [f] Purified by sublimation [150 °C (0.66 Torr)] followed by recrystallization from petroleum ether (60–110 °C). [g] Purified by sublimation [130 °C (0.8 Torr)].

Scheme III



chromene formation. We hold that this uniqueness is due to the intervention of a sigmatropic process as shown in path B (Scheme III) which, by virtue of the mechanism, can lead only to 2*H*-chromenes. Thus, the lack of five-membered rings from 1 and the hydration of 1-phenyl-4-(*p*-bromophenoxy)-1-butyne are readily accommodated. The apparent hydration reaction leading to the butanone derivative most probably involves hydrolysis of an intermediate vinyl trifluoroacetate, either by fortuitous moisture during the reaction or during the aqueous workup.

Conversion of 2 into 3 seemingly does not involve a Friedel–Crafts type alkylation as the expected site of charge formation (and, therefore, the site of attachment of the aromatic ring in 2) is the tertiary benzylic position, not the observed site.[23] Claisen rearrangement to 8 followed by ring



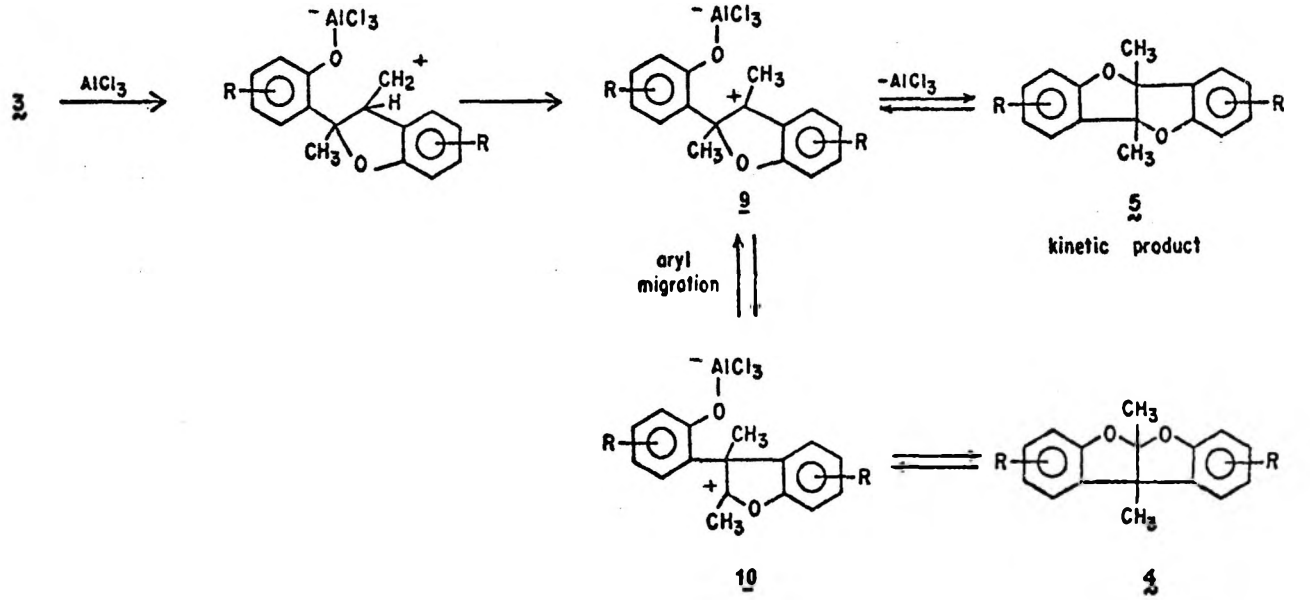
closure to 3 readily explains the site of attachment of the aromatic ring. 2-Allylphenols are well known to produce 2-methyl-2,3-dihydrobenzofurans under acidic conditions.[17,18]

Rearrangements of phenyl allyl ethers have been reported to be catalyzed by such hard Lewis acids as $TiCl_4$ and BF_3,[18c] which probably catalyze the reaction by coordination to the heteroatom. The present case is the first example of catalysis by a soft Lewis acid. This distinction is a very important one, as the site of coordination influences not only the efficacy of the catalyst but also the likelihood that the catalyst will induce other processes. For example, hard Lewis acids can promote not only Claisen rearrangement, but also ionic ring contraction as discussed below. In addition to Claisen rearrangement, soft Lewis acids may also promote double bond isomerization and/or migration.[18c]

It should be pointed out that the differing efficacy of Ag(I) and Hg(II) in rearranging alkene and alkyne substrates demonstrates that these reagents are indeed interacting at the unsaturated sites. Although heavy metal–ether and heavy metal–arene complexes are well known,[19] these complexes cannot be responsible for catalytic activity, as one would expect no difference in reactivity of alkenes and alkynes or at best reactivity paralleling thermal behavior, i.e., more facile rearrangement of alkene substrates, a phenomenon contrary to our findings. The rate enhancement of rearrangement in these cases is actually due to the metal ions, as sodium tetrafluoroborate (and sodium trifluoroacetate) as well as fluoroboric acid (as the diethyl ether complex) and trifluoroacetic acid have no effect on **1b** under conditions in which the corresponding silver(I) and mercury(II) salts completely isomerize **1b**. The failure of Ag(I) and Hg(II) to promote rearrangement of 3 into 4 may be taken as evidence that the site of coordination of 1 with these species is not the oxygen atom (see below).

$AlCl_3$ Catalyzed Reactions. Although we have been unable to isolate or detect intermediates in the $AlCl_3$ catalyzed conversion of 1 into 4, it is reasonable to assume that 1 proceeds to 4 in a stepwise manner via 2 and 3.[20] These transformations may be charge-induced Claisen rearrangements similar in mechanism to the process reported for BCl_3.[2] A mechanism accounting for the transformation of 3 into 4 is proposed in Scheme IV. Aluminum chloride promoted ether

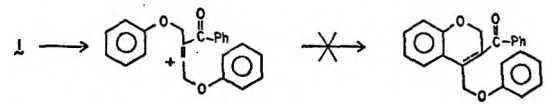
Scheme IV



cleavage in **3** would produce a primary cation which might be expected to readily rearrange to the more stable tertiary benzylic ion **9**. Kinetically controlled ring closure of **9** would produce **5**. However, in a thermodynamically controlled process the ion **9** may rearrange to **10**, which gives **4**, the apparent thermodynamic product, on ring closure.

Although neither the reaction of pterocarpin nor homopterocarpin (3,9-dimethoxy-6*H*-benzofuro[3,2-c]-6a,11a-dihydrobenzopyran) with aluminum chloride has been investigated, it is interesting that in the presence of aqueous HCl these compounds, which differ from **3** only by the absence of the 11a-methyl group, undergo fission of the five-membered ring, giving 2*H*-chromene derivatives.[21] We are in the process of examining the reaction of pterocarpins with aluminum chloride to understand this dichotomy.

The lack of formation of **4** in reactions conducted in the presence of soft Lewis acids may be readily explained. Formation of **4** most likely entails coordination of $AlCl_3$ with an oxygen atom, a hard base site. Since soft Lewis acids will have less propensity to coordinate with such sites, reactions involving soft acids should stop at **3**, as observed.



11

This interpretation is borne out by the fact that **1b** with $AgBF_4$ gives only **3b**, whereas the same reaction conducted in the presence of benzoyl chloride (presumably with $PhCO^+BF_4^-$ as the acid) produces **4** cleanly. Acylium ions are classified by Pearson[3] as hard acids. This result has additional significance because it provides some support for the assumption that hard acids are inducing rearrangement by coordination with a heteroatom rather than coordination with unsaturated sites. Benzoyl chloride has been reported[22] to undergo Friedel–Crafts reaction with a variety of alkynes in the presence of $AgBF_4$ or $AlCl_3$. If coordination in **1** was taking place at the triple bond, one would expect irreversible incorporation of the benzoyl function into the reaction product, i.e., **11**, a process we have not observed.

Research is in progress to further elucidate the mechanism of the conversion of **3** into **4** using deuterated samples, to extend the **1** → **4** conversion to the sulfur and nitrogen analogues of **1**, and to correlate the catalytic efficacy of metal salts to π complex stability constants.[25]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Spectral data were collected as follows: IR, crystallized melts unless otherwise specified, Perkin Elmer 435B; NMR, $CDCl_3$, Me_4Si reference (δ 0.00), Varian T-60; mass spectra, Varian M-77. Microanalyses were performed by Mr. Mike Gilles in the Michigan Technological University microanalytical laboratory.

The 1,4-bis(aryloxy)-2-butynes were prepared by standard methods and characterized by comparison of NMR and melting points to literature values. The following data were collected for new derivatives of **1**. 1,4-Bis[3-(trifluoromethyl)-4-nitrophenoxy]-2-butyne (**1f**): mp 94–95 °C (C_2H_5OH); NMR δ 8.15–7.95 (2 H, d, J = 9 Hz), 7.50–7.10 (4 H, m), 4.95 (4 H, s). Anal. Calcd for $C_{18}H_{10}F_6N_2O_6$: C, 46.57; H, 2.15; N, 6.03. Found: C, 46.48; H, 2.14; N, 5.94. 1,4-Bis(3,4-methylenedioxyphenoxy)-2-butyne (**1c**): mp 81–82 °C (C_2H_5OH); NMR δ 7.05–6.35 (6 H, m), 6.10 (4 H, s), 4.77 (4 H, s). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.00; H, 4.30. The only new 2*H*-chromene prepared in this study was **2c**, which was obtained as a mixture of isomers that could not be conveniently separated: 59% yield; mp 190–210 °C (C_2H_5OH); NMR δ 6.80–6.40 (4 H, d), 6.00–5.95 (4 H, d), 4.68–3.75 (3 H, s superimposed on m), 2.25–2.00 (methyl H's, broad multiplet with spikes at 2.22, 2.15, 2.12, and 2.05). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.02; H, 4.31. 2*H*-Chromenes for comparison samples were prepared by the method of Thyagarajan and Majumdar.[10]

General Procedure for the Reaction of 1 with Soft Lewis Acids. To the appropriate salt (0.5–1.0 molar equiv) in dichloromethane (~5 mmol/mL) was added, in one portion, solid **1**. After the reaction times indicated in Table I the reaction mixture was filtered through a pad of neutral alumina eluted with dichloromethane. The eluent was then concentrated in vacuo to give the product. Recrystallization of this material from petroleum ether (60–110 °C) gave the pure compound, identified by comparison (mp, IR, NMR) with authentic samples.

General Procedure for the Preparation of 4. To a stirred solution of **1** (3 g) in dichloromethane (50 mL), under N_2, was added in one portion an equimolar amount of $AlCl_3$. Immediately an intensely colored solution formed (usually green or red) and after a few minutes the reaction mixture began to gently reflux. After stirring an additional 30 min, 3 N HCl (25 mL) was cautiously (frothing) added. The organic layer was collected and washed successively with water (50 mL), 10% NaOH (50 mL), and again with water (50 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give the products listed in Table II. Recrystallization from petroleum ether (60–110 °C) gave analytical samples.

Reaction of 1b with $AgBF_4$ and Benzoyl Chloride. To **1b** (1.5 g) in dichloromethane (30 mL), under N_2, was added benzoyl chloride (1 molar equiv) followed immediately by solid $AgBF_4$ (1 molar equiv). At this point some fluoroboric acid vapors were noted. The reaction mixture was then stirred (1–24 h, depending on **1**). The filtered reaction mixture (green to blue in color) was washed with 3 N HCl (25 mL) followed successively by water (50 mL), 10% KOH (25 mL), and water (50 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give a 40% yield of **4b** identical in all respects with the material obtained in the $AlCl_3$ catalyzed reaction of **1b**.

Conversion of 3g and 5g into 4g. Compound **3g** (1.5 g) was added to a slurry of $AlCl_3$ (0.5 g) in CH_2Cl_2 (15 mL) under a blanket of N_2. A red color developed immediately and after 5 min the solution gently refluxed. After stirring 35 min the reaction mixture was quenched by cautious addition of 3 N HCl (organic phase became colorless) and worked up as above to give **4g** (67%). Similar reaction of **5g** also gave a blood red solution and an exotherm developed. Workup as above gave a quantitative yield of a solid containing ~85% **4g** and ~15% unreacted **5g** (by NMR integration).

Preparation of 1-Phenyl-4-(*p*-bromophenoxy)-1-butyne. To a solution of phenylacetylene (1.16 g, 0.0114 mol) in dry dioxane (20 mL) was added 4.6 mL of 2.48 M butyllithium (0.0114 mol in hexane). The mixture was heated to reflux and solid 2-(*p*-bromophenoxy)ethyl *p*-toluenesulfonate (4.12 g, 0.0111 mol) was added portionwise to the dark solution. Approximately 4 mL of liquid was distilled away; the remaining solution was refluxed for 11 h during which time a voluminous precipitate formed. The cooled mixture was diluted with water (100 mL) and extracted with ether (3 × 50 mL). The combined extracts were successively washed with water and brine, and the organic phase was then dried ($MgSO_4$). Solvent removal in vacuo gave a yellow oil which crystallized on standing (1.86 g, 56%). Recrystallization from hexane gave an analytical sample: mp 46.5–48 °C; IR (NaCl, melt) 3050, 2925, 1590, 1490, 1295, 1245, 1180, 1080, 1040, 1005, 830, 760, 700 cm^{-1}; NMR δ 7.33–7.00 (7 H, m), 6.57 (2 H, d, J = 9.0 Hz), 4.05 (2 H, t, J = 8.0 Hz), 2.77 (2 H, t, J = 8.0 Hz). Anal. Calcd for $C_{16}H_{13}BrO$: C, 63.80; H, 4.36. Found: C, 63.85; H, 4.33.

Reaction of 4-(*p*-Bromophenoxy)-1-phenyl-1-butyne with Mercuric Trifluoroacetate. To a solution of 0.30 g (1.00 mmol) of 4-(*p*-bromophenoxy)-1-phenyl-1-butyne in dry (distilled from and stored over CaH_2) THF (2 mL) was added solid mercuric trifluoroacetate (0.44 g, 1.03 mmol) portionwise over 1 min. After stirring at room temperature for 1 h the solution was refluxed for an additional 4.5 h. The cooled solution was treated with 25 mL of an alkaline $NaBH_4$ solution (1 g of $NaBH_4$, 0.5 g of NaOH). The mixture was filtered and the filtrate was extracted with chloroform (2 × 50 mL). The combined chloroform extracts were dried ($MgSO_4$) and the solvent was removed in vacuo. The yellow oil thus obtained was purified by preparative layer chromatography (SiO_2/3:2 hexane–benzene), giving 55 mg of recovered starting material and 110 mg (42%) of the butanone: mp 71–72 °C (cyclohexane); NMR δ 8.2–6.6 (9 H, m), 3.93 (2 H, t, J = 6.0 Hz), 3.07 (2 H, t, J = 6.0 Hz), 2.13 (2 H, apparent quintet, J = 6.0 Hz). Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.18; H, 4.74. Found: C, 60.43; H, 4.68.

Repetition of this experiment in CH_2Cl_2 and in THF in the presence of acid or water scavengers (CaO, HgO, 4Å molecular sieves) altered the reaction rate but not the major product.

Reaction of 4-(*p*-Bromophenoxy)-1-phenyl-1-butyne with Mercuric Acetate. To a hot solution of 2.17 g (10 mmol) of HgO in 11 mL of glacial acetic acid was added 3.01 g (10 mmol) of 4-(p-bromophenoxy)-1-phenyl-1-butyne in glacial acetic acid (6 mL) over 5 min. After an additional 5 h of heating over a steam bath, the mixture

Table III. Relative Percentages of 2, 6, and 12 Produced by Hydration of *1*[a]

substituent (in 1)	chromene	registry no.	6	registry no.	12	registry no.
4-OMe	100	67238-38-4	0		0	
2-OMe	100	38532-35-3	0		0	
2-Br[b]	18	37104-76-0	51	67238-39-5	31	67238-43-1
2-Cl	16	37104-72-6	56	67238-40-8	28	67238-44-2
4-Cl	11		52	67238-41-9	37	67238-45-3
2,4-diCl	0		84	67238-42-0	16	67238-46-4

[a] By integration of NMR spectrum of crude reaction mixture. Physical and spectral data for new compounds appear in Table IV. [b] Registry no.: 37104-64-6.

Table IV. Physical and Spectroscopic Data for 6 and 12[c]

R (in 1)	product	mp, °C	NMR (aromatic portion deleted)
2-Br	6	95–97	4.74 (2 H, s), 4.55–4.25 (2 H, t, J = 6 Hz), 3.35–3.05 (2 H, t, J = 6 Hz)
2-Cl	6	96–97	4.71 (2 H, s), 4.45–4.20 (2 H, t, J = 6 Hz), 3.30–3.00 (2 H, t, J = 6 Hz)
4-Cl	6	93–94	4.66 (3 H, s), 4.45–4.20 (2 H, t, J = 6 Hz), 3.20–2.95 (2 H, t, J = 6 Hz)
2,4-diCl	6	99–100	4.75 (2 H, s), 4.50–4.25 (2 H, t, J = 6.4 Hz), 3.30–3.00 (2 H, t, J = 6.4 Hz)
2-Br	12	[132–133 (0.007)][b]	4.57 (2 H, s), 3.85–3.60 (2 H, t, J = 6 Hz), 3.30 (3 H, s), 3.00–2.75 (2 H, t, J = 6 Hz)
2-Cl	12	[115 (0.004)][b]	4.60 (2 H, s), 3.85–3.55 (2 H, t, J = 6 Hz), 3.29 (3 H, s), 3.00–2.70 (2 H, t, J = 6 Hz)
4-Cl	12	27	4.63 (2 H, s), 3.85–3.60 (2 H, t, J = 6 Hz), 3.37 (3 H, s), 2.95–2.70 (2 H, t, J = 6 Hz)
2,4-diCl[a]	12	43–44	4.60 (2 H, s), 3.80–3.55 (2 H, t, J = 5 Hz), 3.28 (3 H, s), 2.95–2.65 (2 H, t, J = 5 Hz)

[a] Obtained from the corresponding 6 by refluxing in acidic methanol. [b] Boiling point (Torr). [c] Satisfactory analytical data were reported for the compounds.

was extracted with chloroform (2 × 100 mL). The combined chloroform extracts were washed with 10% K_2CO_3 solution until neutral and then with water (100 mL). The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was chromatographed on SiO_2 to give 2.4 g (75%) of the ketone described above.

General Procedure for Hydration of 1. Mercuric oxide (6.75 g, 0.03 mol) was dissolved in a solution of concentrated sulfuric acid (5.3 mL) and water (20 mL). After stirring for about 5 min at 25 °C the solution was diluted with methanol (25 mL) [note: bright opaque yellow color formed]. The mixture was then heated to reflux and 1,4-bis(aryloxy)-2-butyne (1 molar equiv based on HgO) in tetrahydrofuran (60–80 mL) was then added in one portion. After 12–18 h at reflux, the cooled solution was filtered and evaporated in vacuo to one-tenth of the original volume. After dilution with water (1 L) and extraction with ether (3 × 150 mL), the combined organic phase was washed successively with water (100 mL), 5% potassium hydroxide solution (200 mL), and water (100 mL). Drying ($MgSO_4$) and solvent evaporation gave the crude product. The NMR spectrum was used to give the relative amounts of **2**, **6**, and 1-aryloxy-4-methoxy-2-butanones (**12**) indicated in Table III. Subsequent chromatography on silica gel eluted with hexane gave the chromene derivative. Elution with chloroform gave a mixture of **6** and **12** which was readily separated by refluxing in hexane (selectively dissolving the oily **12** from crystalline **6**). Recrystallization or distillation then gave analytically pure samples having the spectral and physical properties listed in Table IV. The 1-aryloxy-4-methoxy-2-butanones (**12**) arise from **6** presumably via an acid-catalyzed β elimination/Michael addition sequence. Prolonged reflux completely converts **6** to **12**.

Acknowledgments. We wish to thank the Research Corporation for support of this research and one of us (M.C.J.) would particularly like to express gratitude for receiving a summer stipend. We wish to thank Dr. R. Caple, University of Minnesota, Duluth, for bringing ref 22 to our attention. Robert Braem of the Fish and Wildlife Service, Marquette, Mich., kindly provided a generous gift of sodium 4-nitro-3-trifluoromethylphenoxide (TFM lampricide).

Registry No.—**2c** isomer I, 67238-47-5; **2c** isomer II, 67238-48-6; **3g**, 14270-20-3; **5g**, 3988-23-6; 1-phenyl-4-(*p*-bromophenyloxy)-1-butyne, 67238-49-7; phenylacetylene, 536-74-3; 2-(*p*-bromophenoxy)ethyl *p*-toluenesulfonate, 67238-50-0; 1-phenyl-4-(*p*-bromophenoxy)-1-butanone, 67238-51-1.

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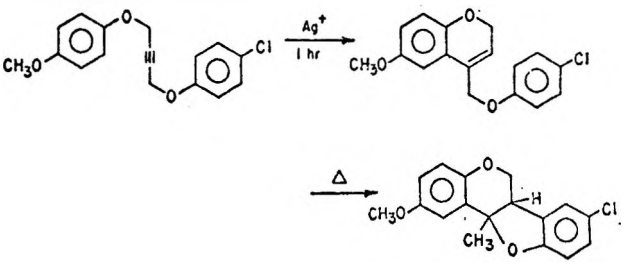
(8) This charge-induced process should allow one to selectively form **3** having the more electron rich aromatic residue fused to the 6-ring with the other aromatic residue fused to the 5-ring, e.g.,



Such selectivity is not possible in the direct thermal process due to the lack of a pronounced substituent effect in the Claisen rearrangement; cf. S. J. Rhodes and R. Rollins, *Org. React.*, **22**, 1 (1975).
(9) Iron(III) chloride was a less effective catalyst (in CH_2Cl_2), reacting slowly with **1b** to give **4b** as the sole product. Boron trifluoride etherate (in CH_2Cl_2) was even less effective, giving ~5% conversion to **4b** after 24 h. Zinc chloride was without effect on **1**, while $SbCl_5$ caused extensive, rapid decomposition to unidentified compounds.
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(16) (a) This process is isoelectronic with the Fodor modification of the Bischler–Napieralski reaction, i.e., transformation of nitrilium ions into 3,4-dihydroisoquinolines. (b) The Bischler–Napieralski reaction has been successfully applied to the formation of seven-membered rings [3,4-dihydro-5*H*-benzazepines, cf. Y. Kanaoka, E. Sato, O. Yonemitsu, and Y. Ban, *Tetrahedron Lett.*, **No. 35**, 2419 (1964)].
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(18) Initial results indicate that phenyl allyl ether does not undergo similar rearrangement in the presence of $AgBF_4$ or $Hg(O_2CCF_3)_2$; however, this and similar cases are presently under investigation. Phenyl allyl ethers have available at least three alternative reaction modes in addition to Claisen rearrangement: (a) isomerization into thermodynamically more stable vinyl ethers [cf. J. M. Reuter and R. G. Salomon, *J. Org. Chem.*, **42**, 3360 (1977)]; (b) simple ether cleavage [J. F. W. McOmie, J. Watts, and D. West, *Tetrahedron*, **24**, 2289 (1968)]; and (c) Claisen rearrangement with [H. Hui and H. Yip, *J. Polym. Sci., Polym. Chem. Ed.*, **14**, 2689 (1976)] or wi-

thout subsequent polymerization [K. Narasaka, E. Balk, and T. Mukaiyama, *Chem. Lett.*, 1041 (1975)]. The factors controlling reactivity of a substrate in any given reaction mode are unknown and at present the behavior of a given substrate under a particular set of reaction conditions cannot be predicted.

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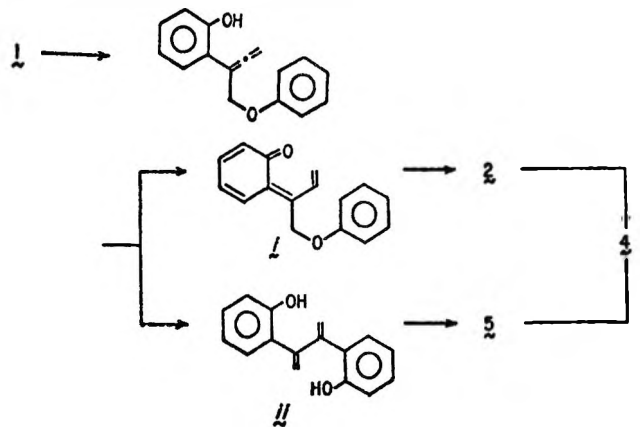
(20) An alternative mechanism involving direct formation of **5** from **1** by a "double" Claisen rearrangement followed by ionic rearrangement as shown below may be excluded from consideration. If this mechanism was operating one might expect to isolate **5** from reaction of **1** with heavy metal ions. Additionally, the absence of **5** in all crude $AlCl_3$ catalyzed reaction mixtures, even when the reaction was interrupted at low conversion, makes this path seem unlikely. It would appear that the 1,5-hydrogen shift leading to i is faster than the 3,3 process leading to ii. Schmid (ref 2) has indicated that the initial thermal rearrangement is slower than the 1,5-hydrogen shift in the rearrangement of phenyl propynyl ethers into 2*H*-chromenes.



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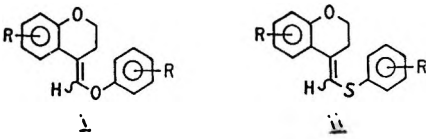
(23) As pointed out by a referee, the spirocyclic intermediate produced by the Friedel–Crafts process could be formed reversibly. On this basis it was suggested that the observed mode of fusion might ultimately prevail. However, under equilibrating conditions, formation of charge at the benzylic position would most probably result in formation of the vinyl ether, i, or



products derived from it (rather than from **2**). Support for this contention derives from the well-known thermodynamic stability of vinyl ethers over allyl ethers. Additionally, treatment of the related sulfur system ii with trifluoroacetic acid in refluxing chloroform produces the corresponding vinyl sulfide in excellent yield (ref 23b) presumably via a benzylic cation. We therefore do not consider formation of **2** by a Friedel–Crafts type alkylation likely. (b) B. S. Thyagarajan, K. C. Majumdar, and D. K. Bates, *J. Heterocycl. Chem.*, **12**, 59 (1975).

(24) Reactions at the triple bond of aryl 2-propynyl ethers have also been sought but not found. Thus, phenyl 2-propynyl ether reacts with $PhCO^+ AlCl_4^-$ producing 4-benzoylphenyl 2-propynyl ether in good yield. When the 4 position of the ether is blocked, ether cleavage producing the aryl benzoate occurs: unpublished observations of M. Dziobak, 1978.

(25) This paper is dedicated to the memory of Professor H. Schmid.

Reactions of Ketones with Sodium Hydride or Potassium Hydride in the Presence of Trimethylsilyl Chloride. Preparation of Trimethylsilyl Enol Ethers[1]

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Reactions of cyclohexanone with NaH and Me_3SiCl in various solvents yielded predominantly (90–97%) the silyl enol ether **2** resulting from enolization, with only a few percent of the alkyl silyl ether **1** resulting from initial reduction. Similar reactions with KH and Me_3SiCl proceeded well only in dioxane to give >99% of **2**. Cyclohexanone, 2-methylcyclohexanone, acetophenone, and 2-heptanone were converted to trimethylsilyl enol ethers in good yields by this method.

Alkali metal hydrides are widely used as bases in organic synthesis and have been especially useful for the conversion of carbonyl compounds to metal enolates.[3–5] Sodium hydride has been most commonly used.[3] Potassium hydride has recently been shown to be much more reactive than sodium hydride and is an excellent reagent for the generation of potassium enolates.[4] Lithium hydride, although comparatively unreactive, has been used in a few cases to generate lithium enolates.[5]

Some hydrides of other metals, particularly complex metal hydrides such as $NaBH_4$ and $LiAlH_4$, are widely used as reducing agents in organic synthesis;[6] these hydrides will usually reduce a carbonyl group rather than abstract an enolizable hydrogen. In contrast, alkali metal hydrides have been reported to reduce organic compounds relatively infrequently.[7–10] Reductions of carbonyl groups have been reported only in special cases; for example, sodium hydride has been shown to reduce carbonyl compounds which have no enolizable hydrogens or which are not readily enolized.[7]

The reactions of alkali metal hydrides with carbonyl compounds to give metal enolates are commonly believed to be catalyzed by alkoxides (formed from traces of alcohol impurities in the reaction mixtures) as the proton-transfer agents,[3c,i] since the hydrides are insoluble in common organic solvents.[4c,11] Thus, catalytic amounts of ethanol have been used to initiate sluggish reactions of metal hydrides.[3c,4e] We were intrigued by the possibility that the reactions of ketones with alkali metal hydrides might proceed by initial *reduction* of a small fraction of the ketone to the corresponding alkoxide, which would then catalyze enolate formation by acting as the proton-transfer agent (Scheme I). We have therefore studied the reactions of several ketones with sodium, potassium, and lithium hydrides in the presence of trimethylsilyl chloride, a reagent expected to trap enolate anions or alkoxide anions as they are formed.[12,13] To the extent that reduction takes place, an alkyl trimethylsilyl ether (e.g., **1**) should be formed; to the extent that direct enolization takes place, an alkenyl trimethylsilyl ether (trimethylsilyl enol ether, e.g., **2**) should be

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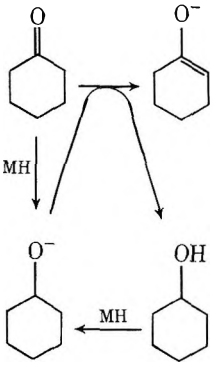
Table I. Reactions of Cyclohexanone with MH/Me_3SiCl

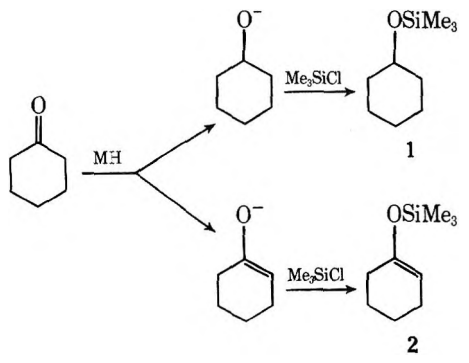
MH	solvent[b]	% yields[a] of 1 and 2 at various reaction times: 2 h 1	2 h 2	12 h 1	12 h 2	24 h 1	24 h 2
LiH	dioxane	0.1	0.1	5.6	4.1	16	11
LiH	THF	0.04	0.04	2.3	2.8	3.6	3.0
NaH	hexane	0.2	30	4.0	73	4.9	95
NaH	heptane	2.6	108[c]				
NaH	toluene (75–80 °C)	1.3	40	2.7	95		
NaH	toluene	2.3	112[d]				
NaH	dioxane (75–80 °C)	1.4	39	4.7	78	5.0	96[e]
NaH[f]	dioxane	4.6	70	6.3	98		
NaH[f]	dioxane	3.1	68	7.1	104		
NaH[g]	dioxane	3.7	83	5.4	99		
NaH[g]	dioxane	5.3	93	5.5	92		
NaH[g,h]	dioxane	5.2	94	5.8	94		
NaH[i]	dioxane	3.4	100	4.5	105		
NaH	THF	0.1	0.1	0.1	0.3	0.3	16
NaH	DME[j] (75–80 °C)	1.2	9.4	5.9	23		
NaH	DME	0.0	3.3	3.9	44	9.5	63
NaH	DME[j]–HMPA (4:1)	0.1	0.1	7.4	33	16	49
KH	heptane[k]	0.0	3.7	0.0	3.6	0.1	3.4
KH	toluene[l]	0.0	4.9	0.0	4.1	0.1	2.4
KH	dioxane	0.3	106	0.5	99		
KH	dioxane (crown)[m]	0.0	0.1	0.3	84		
KH	THF	0.0	0.9	0.0	2.3	0.0	5.0
KH	THF[j] (crown)[m]	0.0	0.0	0.0	0.0	0.0	0.0[n]

[a] Yields were determined by VPC (SE-30 column)[23] using *n*-undecane as an internal standard (relative detector response calibrated). [b] At reflux temperature unless otherwise indicated. See Experimental Section for purification of solvents and general procedure. [c] A sample taken after 1 h was similar. [d] Sample taken at 1 h. [e] Sample taken at 18 h. [f] Supplied by Alfa Inorganics, 57% dispersion in mineral oil. [g] Supplied by Alfa Inorganics, 50% dispersion in mineral oil. [h] The NaH was washed with three portions of a solution of naphthalene in THF (distilled from sodium/benzophenone) to remove traces of sodium metal; a similar reaction in which the NaH was washed with three portions of a solution of naphthalene in DME gave similar results. [i] Supplied by Research Organic/Inorganic Chemical Corp., Belleville, N.J., 50% dispersion in mineral oil. [j] Distilled from sodium and lithium aluminum hydride. [k] Distilled from calcium hydride. [l] Distilled (under reduced pressure) from lithium aluminum hydride. [m] 18-Crown-6 (0.01 equiv) added to reaction mixture. [n] A sample taken after 48 h showed no formation of 1 or 2; gas evolution on workup indicated that KH was still present.

Scheme I



formed. In the course of this investigation, we have found conditions under which trimethylsilyl enol ethers can be prepared from ketones in good yields.



Results and Discussion

Reactions of cyclohexanone with alkali metal hydrides in the presence of trimethylsilyl chloride in a variety of solvents are summarized in Table I. Under all conditions in which a significant degree of reaction took place, the product (2) expected from the enolization pathway overwhelmingly predominated over the product (1) expected from the reduction pathway.[14] With potassium hydride in dioxane, the trimethylsilyl enol ether 2 was almost the exclusive product.

The rates of the reactions are seen to be strongly dependent on the solvent used; in no case was a significant conversion to trimethylsilyl ethers observed in the more polar (or better coordinating) solvents THF, DME, or DME–HMPA. In line with these observations, the addition of 18-crown-6 to some of the (KH) reaction mixtures caused a decrease in the initial reaction rate.[15] Reactions with lithium hydride were very sluggish in all solvents studied. Reactions with sodium hydride resulted in good yields of trimethylsilyl ethers in a number of solvents. Reactions with potassium hydride were surprisingly sluggish in all solvents studied except dioxane, in which reaction was fairly rapid.

The reactions of an unsymmetrical ketone, 2-methylcyclohexanone, with sodium hydride and with potassium hydride in the presence of trimethylsilyl chloride were investigated, and the results are shown in Table II. As with cyclohexanone, the major products were trimethylsilyl enol ethers (**4a,b**). Under all conditions, both double bond isomers were formed, that having the more substituted double bond (**4b**) being slightly favored in heptane and toluene, and that having the less-substituted double bond (**4a**) being favored in dioxane.

Since trimethylsilyl enol ethers were formed in good yields

Table II. Reactions of 2-Methylcyclohexanone with MH/Me_3SiCl[a]

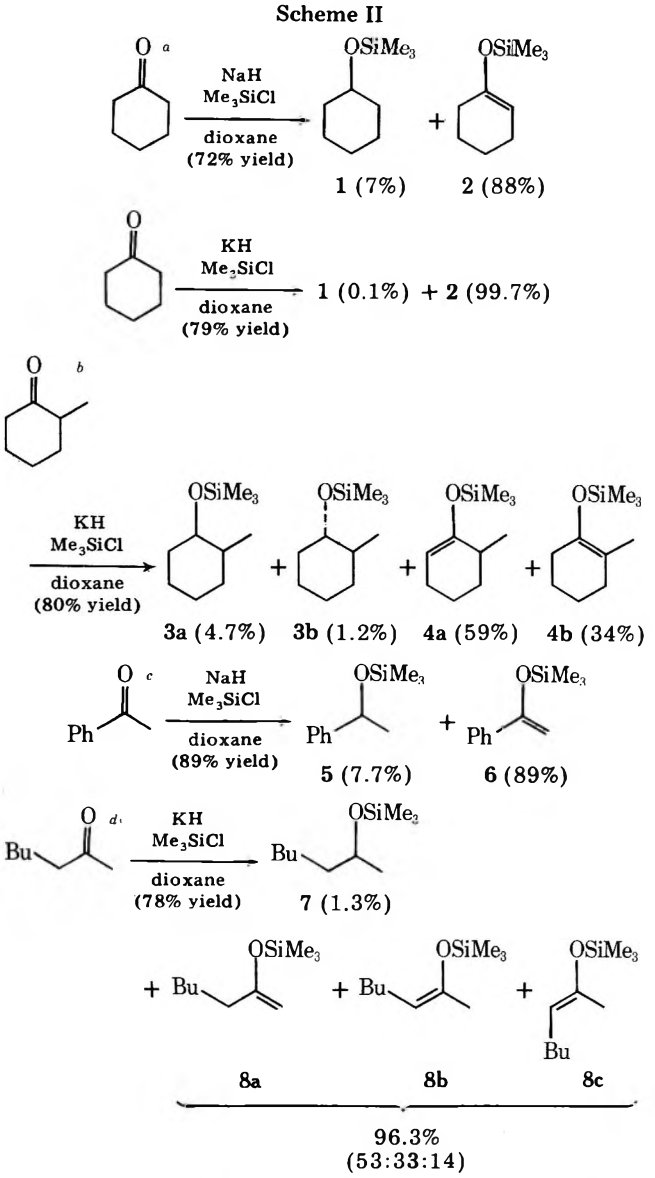
MH	solvent (reflux)	time, h	% product ratios[b] ketone	3a	3b	4a	4b
NaH	heptane	8	3	5	2	25	65
NaH	toluene	6	0	5	3	21	71
NaH	dioxane	12	5	10	3	47	35
KH	dioxane	2	9	3	<1	63	24

[a] See Experimental Section for general procedure. [b] Area ratios determined by VPC (SF-96 column).[23]

under some of the reaction conditions,[16] several ketones were treated with metal hydrides in the presence of trimethylsilyl chloride on a preparative scale to demonstrate the synthetic value of these reactions. The results are shown in Scheme II. The yields represent isolated yields of distilled material. The most favorable conditions for the synthesis of trimethylsilyl enol ethers were found to be KH with Me_3SiCl in dioxane; with NaH the products were usually contaminated with small amounts of reduction product.

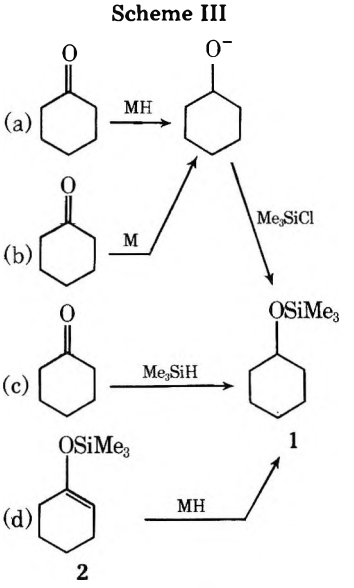
Although *reduction* of the carbonyl group by the alkali metal hydrides (in the presence of trimethylsilyl chloride) is

Scheme II



[a] Registry no.: 108-94-1. [b] Registry no.: 583-60-8. [c] Registry no.: 98-86-2. [d] Registry no.: 110-43-0.

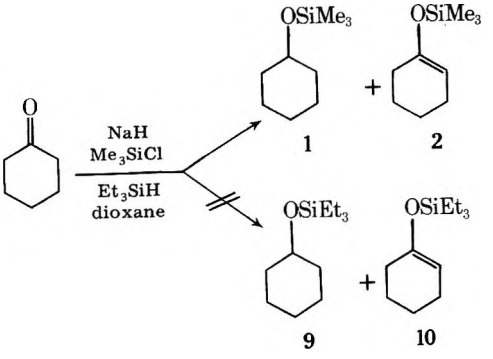
Scheme III



clearly not a major reaction under any of the conditions studied, the products expected from reduction (alkyl trimethylsilyl ethers) were present in measurable amounts under most reaction conditions. In principle, the formation of these products could be accounted for by several pathways (see Scheme III) other than that involving direct reduction of the carbonyl group by the metal hydride (path a).

One possible pathway for the formation of alkyl trimethylsilyl ethers involves reduction of the carbonyl group by an alkali metal impurity (path b). Some commercial samples of alkali metal hydrides have been reported to contain traces of the free alkali metal.[4c,17] Moreover, the reaction of cyclohexanone with sodium in the presence of trimethylsilyl chloride is reported to give a mixture consisting of predominantly 1 and 2.[18] We found that reactions of cyclohexanone with different batches of sodium hydride obtained from different suppliers (in dioxane, in the presence of Me_3SiCl) produced essentially identical ratios of 1 and 2 (see Table I). Moreover, the use of sodium hydride which had been extracted with a solution of naphthalene in THF to remove traces of sodium[8c] gave the same results (see Table I). Therefore, reduction by an alkali metal impurity does not appear to be a major pathway in the formation of the alkyl trimethylsilyl ethers.

Another possible pathway for the formation of alkyl trimethylsilyl ethers involves addition of Me_3SiH (which might be formed by reduction of Me_3SiCl)[19] to the ketone (path c in Scheme III). This pathway was considered unlikely, and was ruled out by conducting the reaction of cyclohexanone with NaH and Me_3SiCl in the presence of Et_3SiH. Neither of the triethylsilyl ethers, **9** or **10**, could be detected in the product



mixture. (A comparison sample of the mixture of triethylsilyl ethers **9** and **10** was prepared by treatment of cyclohexanone with sodium hydride and triethylsilyl bromide in dioxane.)

Finally, production of the alkyl trimethylsilyl ether 1 by reduction of the trimethylsilyl enol ether 2 during the reaction (path d in Scheme III) was ruled out by demonstrating the stability of 2 to the reaction conditions. When 2 was treated with NaH and Me_3SiCl in refluxing dioxane for 36 h, <0.1% of 1 could be detected by VPC.

Since trimethylsilyl chloride is known to trap alkoxides efficiently, the predominance of trimethylsilyl enol ethers in the product mixtures from the reactions of ketones with KH or NaH in the presence of trimethylsilyl chloride indicates that, under these conditions, the metal hydrides are serving primarily as bases for enolate formation, and that reduction is at most a minor side reaction. The reaction rates, at least under some of the conditions, are slower than might be expected on the basis of what is known of the reactions of ketones with NaH and KH in the absence of trimethylsilyl chloride. This in part may be a consequence of poisoning of the metal hydride surface by the trimethylsilyl chloride.[20]

Trimethylsilyl enol ethers are versatile intermediates in organic synthesis.[3h,i,j,21] The use of KH with Me_3SiCl in dioxane for the preparation of trimethylsilyl enol ethers from symmetrical ketones, ketones which can enolize in only one direction, and from unsymmetrical ketones when mixtures are desired, should have some preparative value. The yields are competitive with those of existing methods for the preparation of these compounds, and this method is expected to be applicable to very large-scale reactions. If a few percent of alkyl silyl ether can be tolerated, this method, using NaH, has the feature of being reasonably inexpensive as well. The use of metal hydrides in the presence of trimethylsilyl chloride has potential applicability for the conversion of other compounds with acidic hydrogens into silylated derivatives.[22]

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere, and liquids were transferred with nitrogen-flushed syringes. Only *glass stoppers* were used on reaction flasks.[14] The verb "concentrated" refers to the evaporation of solvent under reduced pressure (water aspirator) using a rotary evaporator.

Vapor-phase chromatographic (VPC) analyses were performed on a Varian Aerograph Model 90-P instrument using helium as the carrier gas at a flow rate of 100 mL/min; retention times were measured relative to that of air.[23]

Infrared (IR) spectra were obtained using a Perkin-Elmer Infracord Model 137 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 spectrometer; chemical shifts are reported in parts per million using chloroform (δ 7.24) as an internal reference.

Materials. Pentane was obtained from petroleum ether (30–60 °C) by shaking with concentrated sulfuric acid, drying over potassium carbonate, and distilling; the fraction boiling below 41.5 °C was used. Hexane was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled from calcium hydride. Unless otherwise indicated, heptane, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride, and toluene and dioxane were distilled under reduced pressure from sodium and lithium aluminum hydride. Trimethylsilyl chloride (Me_3SiCl) and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride. Triethylamine was distilled from barium oxide or from calcium hydride. Lithium hydride was obtained from MC&B Chemicals, Norwood, Ohio. Sodium hydride (dispersion in mineral oil) was obtained from Alfa Inorganics, Beverly, Mass., unless otherwise indicated. Potassium hydride (slurry in mineral oil) was obtained from Alfa Inorganics.

Authentic samples of trimethylsilyl alkyl ethers 1,[18] 5,[24] and 7[25] were prepared by treating the corresponding alcohols with Me_3SiCl and pyridine. A mixture of 3a[26] and 3b[26] [1:3 ratio by VPC (SF-96)[23]] was prepared from 2-methylcyclohexanone by reduction with lithium aluminum hydride in THF (reported to give a 1:3 ratio of cis and trans alcohols),[27] followed by treatment with Me_3SiCl and Et_3N. A sample of silyl enol ether 2[3h,i] was prepared from cyclohexanone by treatment with Me_3SiCl and Et_3N in the presence of $ZnCl_2$.[28] A mixture of **8a**, **8b**, and **8c** [72:24:4 ratio by VPC (Carbowax)[23]] was prepared from 2-heptanone by addition to excess Ph_3CK in DME (forming the kinetic enolate; House and Trost[29] report a 54:37:9 ratio of enolate isomers prepared in this manner), followed by treatment with Me_3SiCl.[30] We thank Dr. Anne M. Hudrlik for providing samples and comparison spectra of silyl enol ethers 6[3i] and 8.[3i]

General Procedure. The experiments described in Table I were carried out in the following general manner. The metal hydride (30–35 mmol) was washed (except for LiH) with three 5-mL portions of pentane, and to the residue were added 15–20 mL of solvent, 0.5 g of undecane (internal standard), 30–35 mmol of Me_3SiCl, and 20–25 mmol of cyclohexanone. The mixture was heated to reflux with an oil bath. After 2 h, a 1-mL portion was withdrawn into a syringe containing 1 mL of Et_3N,[31] and the resulting mixture was added to 30 mL of water overlaid with 10 mL of ether. The aqueous phase was extracted with ether, and the combined organic layers were dried ($MgSO_4$), concentrated, and analyzed by VPC (SE-30).[23] Later samples were taken and analyzed in a similar manner.

The experiments described in Table II were carried out in an analogous manner, except that 2-methylcyclohexanone was used; in most runs decane was present as an internal standard, but the relative detector response for decane and the products was not calculated.

Preparation of 1-(Trimethylsiloxy)cyclohexene (2) using KH. Potassium hydride (5.35 g of a 30% slurry in oil, 40 mmol) was washed with five 10-mL portions of pentane; to the residue were added 30 mL of dioxane, 6.0 mL (5.1 g, 47 mmol) of trimethylsilyl chloride, and 2.46 g (25 mmol) of cyclohexanone, and the resulting mixture was heated at reflux for 7 h. Workup as usual (ether)[33] and distillation yielded 3.35 g (79%) of silyl ether 2 as a colorless liquid, bp 77–80 °C (24 mm) [lit.[3i] bp 74–75 °C (20 mm)].[34,35] VPC analysis (SF-96,[23] column temperature 135 °C; under these conditions *n*-undecane had a retention time of 7.3 min) showed peaks at 1.0 (dioxane, 0.1%), 2.6 (cyclohexanone or cyclohexanol, 0.1%), 4.7 (**1**, 0.1%), and 5.9 min (**2**, 99.7% of peak area).

Preparation of Trimethylsilyl Enol Ethers (4a,b) of 2-Methylcyclohexanone Using KH. Potassium hydride (7.74 g of a 22% slurry in oil, 42 mmol) was washed with three 20-mL portions of pentane; to the residue were added 20 mL of dioxane, 5 mL (4.28 g, 39 mmol) of trimethylsilyl chloride, and 3.26 g (29 mmol) of 2-methylcyclohexanone, and the resulting mixture was heated at reflux for 11 h. Workup as usual (ether)[33] and distillation yielded 4.297 g (80%) of a mixture of silyl ethers **4a** and **4b** as a colorless liquid, bp 73–77 °C (14 mm) [lit.[3i] bp 90–93 °C (20 mm)].[34b,35] VPC analysis (SF-96,[23] column temperature 115 °C; under these conditions *n*-undecane had a retention time of 13.4 min) showed peaks at 0.3 (0.8%), 1.7 (0.1%), 5.6 (2-methylcyclohexanone, 0.8%), 10.5 (**3a**, 4.7%), 11.5 (**3b**, 1.2%), 12.4 (**4a**, 58.6%), and 15.3 min (**4b**, 33.8% of peak area). The NMR integration indicated a 3:2 ratio of **4a** and **4b**.

Preparation of 1-(Trimethylsiloxy)-1-phenylethene (6) Using NaH. Sodium hydride (2.85 g of a 57% dispersion in oil, 68 mmol) was washed with 20 mL of pentane; to the residue were added 40 mL of dioxane, 9 mL (7.7 g, 71 mmol) of trimethylsilyl chloride, and 5.08 g (42 mmol) of acetophenone, and the resulting mixture was heated at reflux for 20 h. Workup as usual (pentane)[33] and distillation yielded 7.23 g (89%) of silyl ether **6** as a colorless liquid, bp 91–97 °C (10 mm) [lit.[3i] bp 89–91 °C (12 mm)].[34] VPC analysis (SF-96,[23] column temperature 160 °C; under these conditions *n*-undecane had a retention time of 11.8 min) showed peaks at 0.9 (dioxane 0.2%), 5.2 (acetophenone, 3.3%), 7.1 (**5**, 7.7%), and 11.5 min (**6**, 88.8% of peak area).

Preparation of Trimethylsilyl Enol Ethers (8a,b,c) from 2-Heptanone Using KH. Potassium hydride (5.75 g of a 50% slurry in oil, 72 mmol) was washed with two 20-mL portions of pentane; to the residue were added 40 mL of dioxane, 9 mL (7.7 g, 71 mmol) of trimethylsilyl chloride, and 4.25 g (37 mmol) of 2-heptanone, and the resulting mixture was heated at reflux for 13 h. Workup as usual (ether)[33] and distillation yielded 5.39 g (78%) of a mixture of silyl ethers **8a**, **8b**, and **8c** as a colorless liquid, bp 74–81 °C (19 mm) [lit.[3i] bp 94–95 °C (52 mm)].[34] VPC analysis (SF-96,[23] column temperature 130 °C) showed peaks at 1.7 (dioxane, 0.1%), 4.6 (2-heptanone, 2.3%), 10.2 (**7**, 1.3%), 10.4, 11.9, and 12.8 (unresolved, **8a,b,c**, 96.3% of peak area), and 29.6 min (0.1% of peak area). VPC (Carbowax)[23] indicated that **8a**, **8b**, and **8c** were formed in a 53:33:14 ratio.[30] The NMR integration indicated a 4:2:1 ratio of **8a**, **8b**, and **8c**.

Treatment of Cyclohexanone with NaH and Et_3SiBr. Sodium hydride (1.1 g of a 57% dispersion in oil, 26 mmol) was washed with three 5-mL portions of pentane; to the residue were added 20 mL of dioxane, 3 mL (3.42 g, 17 mmol) of triethylsilyl bromide, and 1.24 g (13 mmol) of cyclohexanone, and the resulting mixture was heated at reflux for 6 h. Workup as usual (ether)[33] and distillation yielded 2.68 g (100% as **10**) of a mixture of $Et_3SiOSiEt_3$, 9,[18] and 10[18] as a colorless liquid; bp 120–123.5 °C (16 mm) [for **10**, lit.[18] bp 113–114 °C (16 mm)]; IR (film) 6.00, 6.90, 7.37, 7.96, 8.13, 8.42 (strong), 9.36 (strong), 9.86 (strong), 9.99 (strong), 10.15, 11.27 (strong), 12.05 (strong), and 13.4 μm (strong); NMR (CCl_4) δ 0.33–2.17 (br, 40 H), 4.75

(m, 1 H); VPC analysis (SE-30,[23] column temperature 145 °C) showed major peaks at 9.6 ($Et_3SiOSiEt_3$ and **9**, 22% of peak area) and 12.2 min (**10**, 78% of peak area).

Registry No.—**1**, 13871-89-1; **2**, 6651-36-1; **3a**, 39789-14-5; **3b**, 39789-19-0; **4a**, 19980-33-7; **4b**, 19980-35-9; **5**, 14856-75-8; **6**, 13735-81-4; **7**, 53690-75-8; **8a**, 19980-26-8; **8b**, 19980-30-4; **9**, 4419-18-5; **10**, 4342-22-7; $Et_3SiOSiEt_3$, 994-490; triethylsilyl bromide, 1112-48-7; NaH, 7646-69-7; Me_3SiCl, 75-77-4; KH, 7693-26-7.

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(1) Presented in part at the 7th Central Regional Meeting of the American Chemical Society, Morgantown, W.Va., May 1975, Paper no. 124. We thank the National Science Foundation and the Research Council of Rutgers University for their support.

(2) Department of Chemistry, Howard University, Washington, D.C. 20059.

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(9) Combinations of sodium hydride with various transition-metal salts behave as reducing agents toward a number of functional groups; see J. J. Brunet and P. Caubère, *Tetrahedron Lett.*, 3947 (1977), and references cited therein; see also B. Loubinoux, R. Vanderesse, and P. Caubère, *ibid.*, 3951 (1977).

(10) In view of the work described here and in view of previous results [J. C. Powers, R. Seidner, T. G. Parsons, and H. J. Berwin, *J. Org. Chem.*, **31**, 2623 (1966)], the reaction of KH with dimethylformamide to yield dimethylamine after hydrolysis (ref 4c) is probably a deprotonation (and decarbonylation) rather than a reduction of the carbonyl group as originally suggested.

(11) In the presence of 18-crown-6, KH is reported to be soluble in THF to the extent of about 2×10^{-5} M: E. Buncel and B. Menon, *J. Am. Chem. Soc.*, **99**, 4457 (1977). The pK_a of H_2 was estimated to be 35.3.

(12) Me_3SiCl has been used as a scavenger for alkoxides in acyloin reactions: K. Rühlmann, *Synthesis*, 236 (1971), and references cited therein; see also J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).

(13) McConaghy and Bloomfield (ref 7c) have studied the reactions of ketones with sodium hydride in the presence of methyl iodide. Ketones which were resistant to enolization gave mixtures of products resulting from reduction (followed by O-alkylation), mono- and di-C-alkylation, and C-alkylation followed by reduction (and O-alkylation), while cyclopentanone gave predominantly C-alkylation with only 0.5% reduction. Earlier, House and Kramar (ref 3d) reported the reactions of two ketones with sodium hydride in the presence of methyl iodide to give only mixtures of C-alkylated products.

(14) In some of our early small-scale runs, employing sodium hydride in THF, the reactions were somewhat faster than those described here and *reduction* (giving **1**) predominated. Control experiments established that these abnormal reactions were obtained only when rubber septa were used, and all subsequent reactions were carried out in glass-stoppered flasks.

(15) The cause of the solvent effects has not been established. Perhaps the reaction of Me_3SiCl with the metal hydride is accelerated by the more polar solvents, and the surface of the hydride becomes coated with metal halide.

(16) Other workers have stated that attempts to prepare trimethylsilyl enol ethers by reacting ketones with NaH[3l] or KH[4c] in the presence of trimethylsilyl chloride (exact conditions not specified) were unsuccessful. These reports are not necessarily at variance with our results, since we find that such reactions are very slow in a number of common solvents (e.g., THF, DME).

(17) In the reaction of 1-phenyl-2-propanone with NaH,[3j] the small amounts of reduction product which were occasionally formed were attributed to traces of Na in certain lots of NaH.[3l]

(18) K. Rühlmann, A. Sitzki, and C. Michael, *Chem. Ber.*, **101**, 285 (1968).

(19) Me_3SiCl is reduced to Me_3SiH by NaH in the presence of dipolar aprotic solvents such as HMPA; A. J. Chalk, *J. Organomet. Chem.*, **21**, 95 (1970); see also H. Jenkner, *Chem. Ztg.*, **85**, 264 (1961).

(20) Other workers have observed instances where Me_3SiCl diminishes the apparent reactivity of NaH[8c] and KH.[4a,c] See also ref 16.

(21) For reviews on the chemistry of silyl enol ethers, see (a) P. F. Hudrlik, in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, 1976, pp 127–159; (b) J. K. Rasmussen, *Synthesis*, 91 (1977).

(22) We have briefly investigated the reactions of butyraldehyde and of γ-butyrolactone with NaH and KH in the presence of Me_3SiCl. Mixtures of products were obtained, and these reactions did not appear to be of preparative value (P. F. Hudrlik, J. M. Takacs, and D. T. Chou, unpublished work). The reactions of carboxylic acids with NaH/Me_3SiCl in THF have been used to prepare acyloxysilanes: I. Kuwajima, T. Sato, N. Minami, and T. Abe, *Tetrahedron Lett.*, 1591 (1976) (see footnote 6 therein).

(23) The following VPC columns were used: SE-30, 10% SE-30 on Chromosorb W, 10 ft × 0.25 in. aluminum; SF-96, 10% SF-96 on Chromosorb W, 20 ft × 0.25 in. aluminum; Carbowax, 25% Carbowax 20M on Chromosorb W, 20 ft × 0.25 in. aluminum.

(24) W. Gerrard and K. D. Kilburn, *J. Chem. Soc.*, 1536 (1956).

(25) W. J. Richter and D. H. Hunnemann, *Helv. Chim. Acta*, **57**, 1131 (1974).

(26) (a) T. Nishishita, M. Yoshihara, and S. Oshima, *Shitsuryo Bunseki*, **20**, 347 (1972); *Chem. Abstr.*, **78**, 83483u (1973); (b) T. Nishishita, M. Yoshihara, and S. Oshima, *Maruzen Sekiyu Giho*, **No. 17**, 60 (1972); *Chem. Abstr.*, **79**, 17654v (1973).

(27) H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965); see also ref 3b, p 63.

(28) (a) Belgian Patent 670 769 (1966); *Chem. Abstr.*, **65**, 5487d (1966); (b) A. Bazouin, J. Dunogues, and M. Lefort, French Patent 1 436 568 (1966); *Chem. Abstr.*, **66**, 18764z (1967).

(29) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(30) The order of elution (**8a** first, **8c** last) on VPC (Carbowax)[23] was the same as that reported by House and co-workers.[3l]

(31) Triethylamine was used to prevent hydrolysis of the silyl ethers on aqueous workup. See ref 3h, 21a, and 32.

(32) P. F. Hudrlik, Ph.D. Thesis, Columbia University, New York, N.Y., 1968.

(33) The reaction mixture was cooled to room temperature, triethylamine was added (1 equiv/equiv of silyl halide used),[31] and the resulting mixture was poured into water overlaid with pentane or ether. The layers were separated, the aqueous phase was extracted with four or five portions of the same solvent, and the combined organic layers were dried ($MgSO_4$) and concentrated.

(34) The IR and NMR spectra of this sample (a) corresponded to those of an authentic sample, and (b) were in agreement with data reported for this compound.

(35) The IR spectrum of this sample was very similar to that shown for this compound in ref 32.

Carbon-13 Nuclear Magnetic Resonance Substituent-Induced Shieldings and Conformational Equilibria in Cyclohexanes[1]

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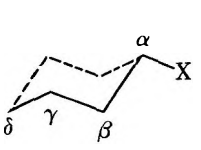
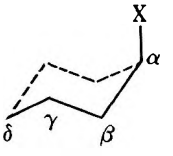
^{13}C NMR shifts induced by the most common hetero substituents are reported for a series of conformationally homogeneous cyclohexanes and alkylated derivatives. The magnitude and in specific cases even the sign of substituent effects on ^{13}C shifts depend strongly on the substitution pattern of the observed alkane. Existing mechanisms and hypotheses for ^{13}C shieldings in hetero-substituted alkanes are examined; only the gross changes in functional carbon (C_α) shifts can be related to MO calculated electron densities, as shown with several norbornane derivatives. The method for measurement of conformational equilibrium constants by low temperature ^{13}C NMR spectroscopy is evaluated. $\Delta G°$ values thus obtained and supplemented by ^1H NMR measurements are discussed for mono- and disubstituted derivatives and compared to literature results and force field calculations.

^{13}C shifts belong to the most important spectroscopic information relating to molecular geometry and charge distribution in carbon compounds.[2] Further development of this promising tool requires the theoretical understanding of shielding mechanisms[3] supported by experimental values as observed with geometrically well-defined model compounds or, at least, a self consistent picture of the experimental shifts, conveniently described as substituent effects $\Delta\nu$ on shielding.[3c] The latter approach should ultimately furnish empirical structure shielding relationships as pioneered for pure hydrocarbons by Grant and co-workers.[4] Before physical significance can be ascribed to postulated relations or before any effects can be applied to unknown molecular structures, it is mandatory to investigate a large number of geometrically related compounds and to analyze the results with more rigorous standards of correlational chemistry.[5]

The shifts observed on α, β, and γ carbons upon introduction of substituents X in the equatorial (e) or axial (a) position of cyclohexane will have the broadest applicability in aliphatic chemistry. **1e** and **1a** contain the most common arrangements of gauche (**1g**) and trans (**1t**) oriented bonds in carbon chains,



1e (1t)

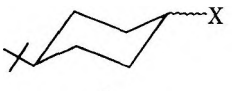


1a (1g)

without substantial deviations from normal sp^3 hybridization. That observation of conformationally inhomogeneous compounds can destroy the inherent information is demonstrated by the results of an earlier study.[6] Here it was reported that for C_α only a very rough correlation exists between substituent X electronegativities (x_p) and shifts, that for C_β and C_γ no relation to X properties exists, and that for C_δ a representation, regarded as satisfactory, as a function of X Taft constants σ^* exists. Ironically, the investigation of conformationally pure cyclohexanes[7] leads to quite satisfactory C_α–x_p correlations (see below); the apparent C_δ–σ^* correlation vanishes, and C_δ, C_β, and eventually C_γ shifts can be represented in terms of electrical field effects[8] depending on X. We have attained conformational homogeneity by either locking cyclohexanes by *tert*-butyl groups and in some cases by methyl groups or by observing cyclohexane conformers at temperatures low enough for slow interconversion on the ^{13}C NMR time scale. The latter approach offers at the same time a promising opportunity to measure conformational equilibria.

Based on the Pople–Karplus approximation of the paramagnetic screening constant,[3a,c] it is often implied or explicitly claimed[9] that ^{13}C shifts in aliphatic compounds show linear dependence on electron densities as available through semiempirical or ab initio quantum mechanical[3b,d,10] calculations. The ambiguities involved, particularly for heavier elements with parametrization of overlap and coulomb integrals,[11] with the possible inclusion of d orbitals and the mixing in of excited states, can lead to serious deviations;[10] but for the very gross changes of functional carbon shifts ($\Delta\nu \sim 60$ ppm from X = H to X = F) a satisfactory correlation to the charge distribution Q is usually obtained. For stereoisomeric 2-norbornanes very similar slopes for *exo*-2- and *endo*-2- compounds are observed with 265 and 269 ppm/e by INDO[11] (Figure 1); correlations of similar quality ($r = 0.98$; $\psi = 22\%$) are obtained with CNDO/2 calculated[11] charges (334 or 338 ppm/e, respectively). Substituent effects on β or γ carbon atoms, however, which are more reliable for stereochemical assignments (see below), fail to show any meaningful relation to CNDO/2 or INDO calculated charge densities[10] (Figure 2). The inadequacy of the available approximate wave functions to reproduce the stereochemically significant shieldings is not unexpected since even within the ground state limitation the Mulliken population would be required accurate to at least 1% on the 200–300 ppm/e scale. Another approach by calculation of classical electric field effects seems to hold more promise[12a] at the present time.

Preliminary results had shown that the magnitude and even the sign of substituent effects can change upon introduction of additional alkyl groups in the α, β, or γ positions. We therefore have prepared and measured cyclohexanes of types **1–7** featuring different substitution patterns on the functional carbon and the observed carbon atoms (Tables I–IV). For



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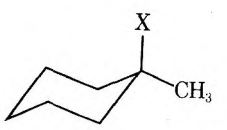

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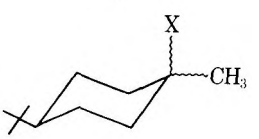

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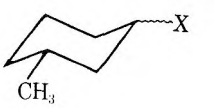

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Table I. Substituent Effects on ^{13}C Shifts[a] in Cyclohexanes (C) and 4-*tert*-Butylcyclohexanes (B)

no.	system	X	pos	registry no.	C_α	C_β	C_γ	C_ϑ	C_ϵ	C_ζ	other C[d]
1	C	F	e		64.54	5.56	−3.37	−2.51			
			a	372-46-3	61.10	3.11	−7.17	−2.02			
2	B	Cl	e	13145-48-7	32.69	10.47	−0.46	−1.89	−0.39	−0.20	
			a	13131-74-3	32.30	7.16	−6.89	−0.92	−0.13	−0.20	
3	B	Br	e	5009-37-0	25.00	11.30	0.70	−2.02	−0.33	−0.22	
			a	5009-36-9	27.50	8.12	−6.28	−1.12	−0.33	−0.22	
4	B	I	e	16133-42-9	2.10	13.81	2.40	−2.42	−0.07	−0.02	
			a	16133-41-8	9.50	9.54	−4.50	−0.80	−0.07	−0.02	
5	B	OH	e	21862-63-5	44.13	8.52	−2.27	−1.50	−0.33	0.06	
			a	937-05-3	38.93	5.95	−6.89	−0.59	0.00	−0.06	
6	B	OCH_3	e	15876-31-0	52.90	5.23	−2.01	−0.72	−0.07	−0.12	55.18
			a	15875-99-7	47.70	3.06	−6.30	−0.07	+0.26	−0.12	55.31
7	C	$OSiMe_3$	e	13871-89-1	43.46	8.99	−2.30	−1.95			
			a		39.13	6.05	−7.18	−1.95			
8	C	OOCH	e		44.94	4.32	−2.96	−2.38			160.34
			a	4351-54-6	41.43	2.17	−6.86	−1.99			160.34
9	B	$OOCCH_3$	e	1900-69-2	46.53	4.75	−2.33	−1.50	−0.33	0.00	21.25 (CH_3), 170.09 (CO)
			a	10411-92-4	42.31	3.15	−6.11	−1.05	−0.07	−0.14	21.38 (CH_3), 170.35 (CO)
10	B	$OOCCF_3$	e	7600-15-9	51.77	4.19	−2.37	−1.62	−0.29	−0.03	114.77 (CF_3), 156.25 (CO)
			a	7556-86-7	48.13	2.83	−6.33	−1.16	−0.29	−0.03	114.77 (CF_3), 156.15 (CO)
11	C	$OOCC_6H_5$	e	2412-73-9	45.78	4.45	−2.90	−2.31			164.83 (CO), 130.58 (C_1')
			a		41.95	2.30	−6.67	−2.31			129.67 (*o*), 128.24 (*m*), 132.72 (*p*)
12	B	OTs	e	7453-05-6	55.51	5.49	−2.24	−2.01	−0.46	−0.10	21.51 (CH_3), 144.30 (C_1'), 127.59 (*o*)
			a	7453-04-5	52.22	3.87	−6.66	−1.36	−0.46	−0.10	129.73 (*m*), 135.00 (*p*)
13	C	SH[c]	e	1569-69-3	11.08	10.69	−0.62	−2.44			
			a		8.93	6.07	−7.58	−1.26			
14	B	NH_2	e	2163-34-0	23.91	9.95	−1.62	−1.31	−0.40	0.00	
			a	2163-33-9	18.07	6.50	−7.22	−0.33	−0.20	0.00	
15	B	$HNCH_3$	e	2523-81-1	32.11	6.25	−1.75	−0.72	−0.26	0.00	34.19
			a	2523-80-0	26.78	3.19	−6.56	−0.14	−0.26	0.00	34.19
16	B	$N(CH_3)_2$	e	2523-69-5	37.08	1.72	−1.13	−0.64	−0.33	0.00	41.73
			a	2523-68-4	33.70	2.63	−6.20	+0.33	−0.33	0.00	43.74
17	C	N_3	e	19573-22-9	32.46	4.45	−2.51	−2.51			
			a		29.80	2.04	−6.86	−1.80			
18	C	NC	e	931-53-3	24.86	6.67	−2.64	−1.82			153.78
			a		23.29	3.52	−6.87	−1.82			155.34
19	C	NCS	e		28.31	6.90	−2.48	−2.17			127.16
			a	1122-82-3	25.83	4.29	−6.44	−2.17			128.59
20	B	NO_2	e	7214-34-8	58.02	4.02	−2.42	−1.98	−0.33	0.01	
			a	7214-33-7	53.87	1.72	−5.64	−1.13	−0.33	0.01	
21	B	CH_3	e	4001-94-9	5.66	8.59	−0.18	−0.65	−0.27	0.00	22.75
			a	3325-80-2	0.13	5.54	−6.49	0.13	−0.27	0.00	17.49
22	C	−C≡CH	e		1.65	5.10	−1.79	−2.05			88.65 (C_1'), 68.25 (C_2')
			a	931-48-6	1.01	3.02	−5.82	−1.34			87.29 (C_1'), 70.00 (C_2')
23	C	−CN[c]	e	766-05-2	0.74	2.17	−2.57	−2.57			122.65
			a		−0.56	0.35	−5.11	−1.99			121.99
24	B	H[d]		3178-22-1	26.91	27.42	27.88	48.69	32.63	27.62	

[a] In ppm (±0.05 ppm) relative to X = H; measured with 2 (B; 20% in $CDCl_3$ at 298 K), or, if not available, with 1 (C; 20% in $CFCl_3$ at 180 ± 1 K), unless indicated otherwise. For other data, see supplementary material (Table Ia) and ref 7d. [b] At 170 K, 20% in CF_2Cl_2. [c] At 193 K in $CFCl_3$. [d] Shifts relative to Me_4Si (C_6H_{12}, 27.66 ppm).

acyclic compounds[8] satisfactory correlations to cyclohexanes were achieved only after corresponding substitution patterns in cyclohexanes had become available.

The introduction of substituents in 1–7 can lead to deviation from normal cyclohexane geometry, which, although small, can influence the observed ^{13}C shifts. Recent force field calculations[12b] have shown that, contrary to other suggestions,[13] the conformational changes generated by hetero substituents cannot be consistently correlated with the observed ^{13}C shielding effects. Molecular mechanical calculations[14] as well as ^1H NMR spectra[15] suggest substantial ring puckering near a *tert*-butyl group attached to cyclohexane, although in several crystal structure determinations only small deviations from normal cyclohexane geometry, apart from unusually small C_3–C_4–C_5 bond angles,[16] have been found. Whereas an equatorial methyl group leaves the ring essentially undistorted,[17,18] axial alkyl substituents bend outward and give rise to ring flattening as evident from spectroscopical[15,18] and calculational[12b,14,17] investigations. Correlations between ^{13}C substituent effects in cyclohexanes 1 and the corresponding 4-*tert*-butylcyclohexanes 2 are good ($r \geqq 0.90$; $\psi \leqq 20\%$) for C_α and C_β, but they are less reliable for C_γ and hardly visible for C_δ, which indicates geometry distortions progressing in that order.

α Effects. The inductive nature of the functional carbon C_α–X shielding mechanism is supported by the long standing relation to X electronegativity.[3] With cyclohexanes, correlations of similar quality ($r > 0.97$; $\psi < 27\%$), again with slopes indistinguishable within the error limit for the stereoisomers, are observed[7d] (Figures 3 and 4). Divalent substituents –X–Y fit in the correlation to X electronegativity if the apparent β' effect of Y on C_α, transmitted over the heteroatom X, is subtracted.[19] Experimentally we find for the β' effect by comparison to –XH: OCH_3, 9.5 and 9.6 ppm; SCH_3, 6.8 and 8.4 ppm; $NHCH_3$, 8.2 and 8.7 ppm; $N(CH_3)_2$, 6.6 and 7.8 ppm, respectively, for equatorial and axial –XY positions.

Introduction of a *tert*-butyl group in the 4 position of cyclohexanes leads to a $\Delta\nu$ enhancement on C_α of up to 1.8 ppm.

Table II. Substituent Effects on ^{13}C Shifts[a] in 1-Methyl-4-*tert*-Butylcyclohexanes

no.	X	pos	registry no.	C_α	C_β	C_γ	C_δ	$C_{\beta'}$ (CH_3)
1	F	e	65199-18-0	68.31	5.40	3.70	−1.57	5.84
		a	65199-17-9	60.28	1.40	−5.02	−0.79	5.10
2	Cl	e	25276-10-2	43.29	10.47	3.83	−1.57	10.65
		a	25276-09-9	39.00	5.85	−4.29	−0.79	11.44
3	Br	e	25276-12-4	40.44	10.53	4.15	−1.64	11.50
		a	25276-11-3	38.41	7.21	−3.59	−0.86	13.06
4	I	e	66922-04-1	24.72	14.94	4.09	−1.70	13.97
		a	66922-05-2	26.71	10.05	−1.83	−0.92	16.51
5	OH	e	16980-56-6	43.82	8.13	3.57	−1.05	7.79
		a	16980-55-5	36.26	3.31	−5.02	−0.27	8.71
6	[H[b]	a-CH_3		27.04	32.96	21.39	48.82	17.49]
	[H[b]	e-CH_3		32.57	36.01	27.70	48.04	22.75]

[a] In ppm (±0.05 ppm) relative to the parent *trans*-1-methyl- (axial CH_3 for X position equatorial) and *cis*-1-methyl-4-(*tert*-butyl)-cyclohexanes (equatorial CH_3 for X position axial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] Relative to Me_4Si.

Table III. Substituent Effects on ^{13}C Shifts in 2-Methylcyclohexanes

no.	X	registry no.	α (C_1)	β (C_2)	β′ (C_6)	γ (C_3)	γ′ (C_5)	γ″ (CH_3)	δ (C_4)
1	e-CH_3, e-Cl[a]	28046-83-5	31.31	8.05	10.25	−1.28	−0.33	−2.41	−1.89
	e-CH_3, a-Cl[a]	28046-82-4	31.44	7.07	6.35	−7.65	−7.74	−5.75	−2.39
2	e-CH_3, e-Br[a]	28046-85-7	25.63	8.28	11.39	−0.96	0.68	−0.72	−1.81
	e-CH_3, a-Br[a]	28046-84-6	27.38	6.98	6.25	−6.87	−6.02	−4.16	−2.20
3	e-CH_3, e-OH[a]	7443-52-9	39.99	6.89	8.20	−2.26	−1.60	−3.93	−1.55
	e-CH_3, a-OH[b]	7443-70-1	33.43	3.47	6.25	−8.04	−7.51	−3.25	−1.03
	a-CH_3, e-OH[c]		38.68	6.26	10.87	−2.00	−2.45	−6.57	−1.67
4	e-CH_3, a-$OOCCH_3$[b]	15288-14-9	36.29	1.71	2.81	−7.46	−6.99	−3.97	−1.74
	a-CH_3, e-$OOCCH_3$[c]		41.35	3.34	4.04	−2.39	−2.83	−5.99	−1.15
5	e-CH_3, e-NH_2[b]	931-10-2	20.62	7.69	9.11	−1.80	−1.01	−3.51	−1.08
	e-CH_3, a-NH_2[b]	2164-19-4	14.19	2.75	6.51	−8.63	−7.51	−3.25	−1.09
	a-CH_3, e-NH_2[c]		19.64	6.71	11.13	−3.04		−6.77	−1.67
6	e-CH_3, e-CH_3[d]	6876-23-9	3.85	6.78	9.12	0.35	0.39	−1.95	−0.08
	e-CH_3, a-CH_3[e]	2207-01-4	−2.58	2.36	6.70	−7.39	−6.60	−1.69 (−5.66)	−0.05

[a] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib in supplementary material, no. 9 equatorial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] As in *a* but in $CFCl_3$. [c] As in *b* but relative to no. 9 axial, Table Ib. [d] See footnote *d* to Table IB. [e] See footnote *e* to Table Ib.

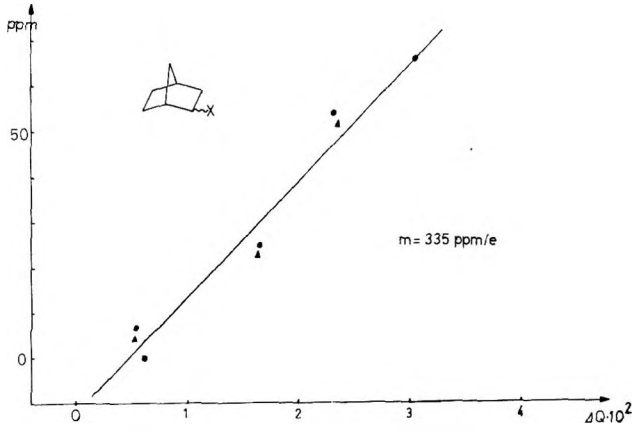


Figure 1. Plot of functional carbon C_2 shifts of 2-norbornane derivatives vs. CNDO/2 calculated electron densities: ● = H, *exo*-CH_3, NH_2, OCH_3, and F; ▲ = H, *endo*-CH_3, NH_2, and OCH_3.

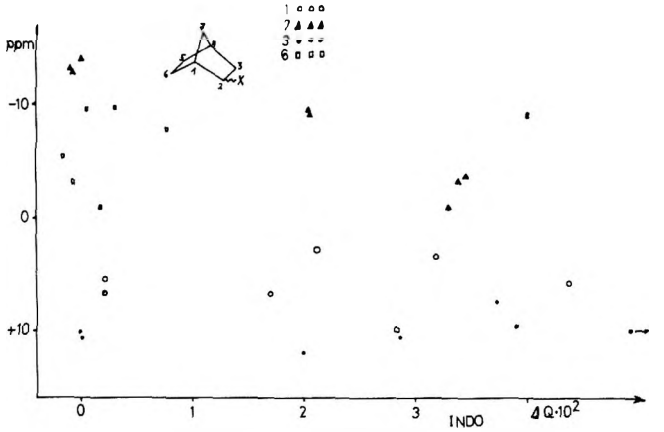


Figure 2. Comparison of C_β and C_γ shifts with INDO calculated electron densities in 2-norbornane compounds.

Since compounds **1** were measured in $CFCl_3$ and **2** in $CDCl_3$ solution at different temperatures, it was secured by control experiments with **2** (X = H, Br, OCH_3) that not more than 0.6 ± 0.2 ppm of $\Delta\nu$ is due to solvent or temperature effects. Methyl substitution at C_3 and C_2 is found to cause variation of the substituent effect of X on C_α by only 5% on the average, but additional alkyl groups at C_1 (α) *enhance* $\Delta\nu$ by up to 23 ppm (**5**; X = I). These findings are at variance with the often assumed general attenuation effect in tertiary compounds or those containing less hydrogen on α or β carbon atoms, as suggested in an early investigation[20] of alcohols and alkanes. Substituent effect enlargements in tertiary as compared to secondary functional compounds of similar magnitude are found in adamantyl[21] and bicyclo[3.3.1]nonyl[22] derivatives; the deviations of $\Delta\nu$ generally increase with increasing X polarizability.

The possible contribution of neighbor group X anisotropies to C_α shifts is limited to a few parts per million,[3a,c,9] as evident from the magnitude of comparable ^1H shifts. Although the concept of isolable bond anisotropy values is questionable[23] and the application of point dipole derived equations on the

Table IV. Substituent Effects on ^{13}C Shifts[a] in 3-Methylcyclohexanes

no.	X	pos	registry no.	α (C_1)	β (C_2)	β′ (C_6)	γ (C_3)	γ′ (C_5)	δ (C_4)	δ′ (CH_3)
1	Cl	e	28046-86-8	31.96	9.90	10.17	−0.01	−1.42	−2.52	−0.52
		a	28046-87-9	32.25	6.32	7.28	−6.80	−7.10	−2.06	−1.58
2	Br	e	28046-88-0	24.16	10.74	11.20	0.28	−0.38	−1.67	−0.78
		a	28046-89-1	26.79	6.91	7.24	−6.09	−6.36	−1.41	−1.11
3	I	e	66922-06-3	0.99	12.89	13.16	2.49	1.83	−2.71	−2.42
		a	66922-07-4	7.88	8.47	9.45	−4.59	−4.80	−2.00	−1.37
4	OH	e	5454-79-5	43.04	8.34	7.31	−1.67	−3.11	−0.89	−0.26
		a	7443-55-2	39.01	5.35	6.14	−6.74	−7.33	−1.93	−0.72
5	CH_3	e[b]	638-04-0	5.92	9.05	8.99	0.08	−0.48	−0.25	
		a[c]	2207-03-6	−0.98	4.75	4.49	−5.22	−6.58	−0.25	−0.55
6	e-CH_3, e-NH_2[d]		1193-16-4	23.15	9.37	9.46	−1.34	−2.33	−1.74	0.19
	e-CH_3, a-NH_2[d]		1193-17-5	18.60	5.87	5.88	−7.40	−7.40	−0.76	−0.58
	a-CH_3, e-NH_2[e]			23.93	8.92	9.91	0.55	−2.71	−2.20	

[a] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib, no. 9 equatorial); measured at 298 ± 1 K, 20% in $CDCl_3$. [b] See footnote *d* to Table Ib. [c] D. Dodrell, C. Charrier, B. L. Hawkins, W. O. Crain, Jr., L. Harris, and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, 67, 1588 (1970). [d] In ppm (±0.05 ppm) relative to methylcyclohexane (Table Ib, no. 9 equatorial); measured at 193 ± 1 K, 20% in $CFCl_3$. [e] As in *d* but relative to no. 9 axial (Table Ib).

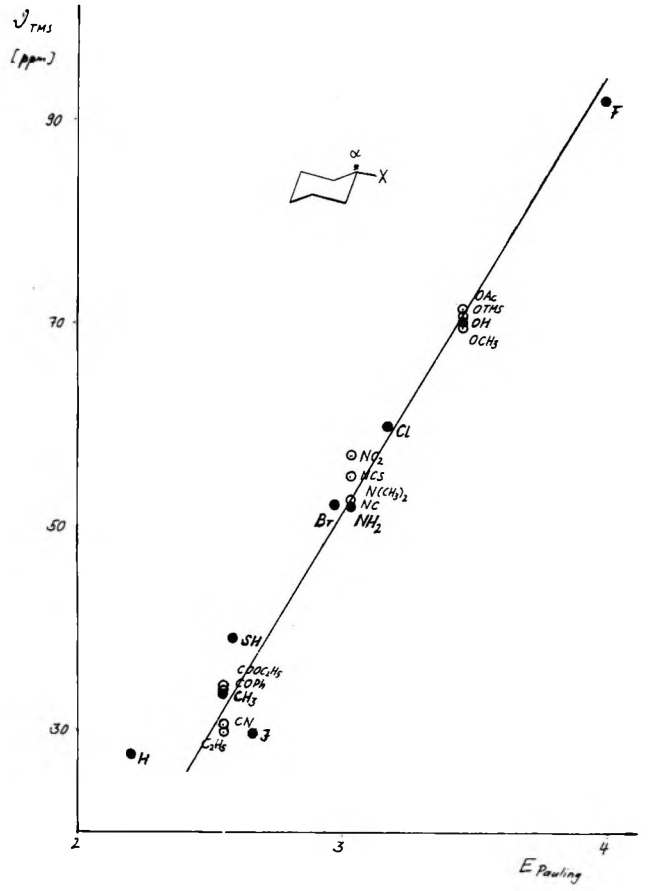


Figure 3. Plot of functional carbon shifts in equatorial-substituted cyclohexanes vs. Pauling electronegativity parameters. Open circles are corrected shifts for second Y at X (see text).

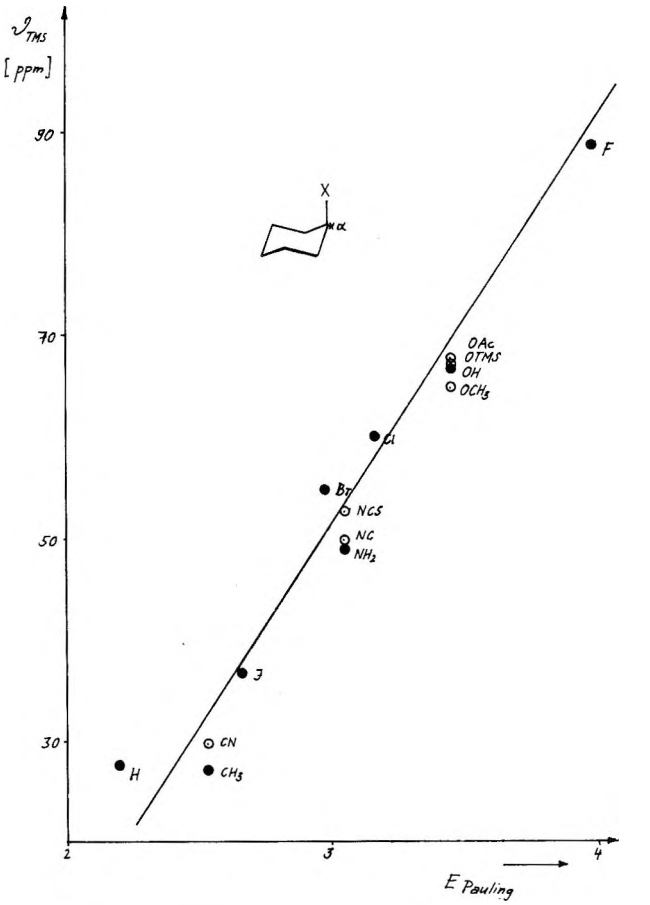


Figure 4. Plot of functional carbon shifts in axial-substituted cyclohexanes as in Figure 3.

screening of nuclei at short distances (as C_α) is misleading,[24] we have estimated some possible anisotropy contributions to C_α shieldings (δ_N) using literature susceptibility values $\Delta\chi$ and standard bond lengths and angles. Following the treatment of ^1H shieldings by ApSimon et al.,[25] we obtain for the C=CH group δ_N = +0.7 ppm (deshielding), for C=O +1.0 ppm, for CH_3 +1.7 ppm, and for -C≡N +2.3 ppm ($\Delta\chi$ = −28 cm^3/molecule[26]).

β Effects. The shifts induced on β carbon atoms are far from being independent of the nature of the substituent X, as had been suggested in earlier investigations.[20,27] Deshielding ranging from 3 to 14 ppm is found in cyclohexanes **1** or **2**; it can be represented quantitatively as the result of a C_β electron cloud distortion by the fluctuating C_α–X dipole (square electric field or van der Waals effect).[12a,28] A striking feature, not rationalized by square electric field effects, is the constantly smaller β effect (by 3–4 ppm) of axial as compared to equatorial C_α–X groups. This stereochemically useful difference, which was already observed in hydrocarbons,[4] is retained in all cyclohexanes, including the tertiary compounds **4** and **5**, as well as in other systems with gauche/trans arrangements of type **1a** and **1e**.[29] The smaller β carbon deshielding in gauche fragments cannot originate in different charges at C_α since the observed difference in $\Delta\nu$ for C_β does not correlate with C_α shift differences between axial and equatorial X pairs, and secondly the β′ effect on CH_3 in **4** and

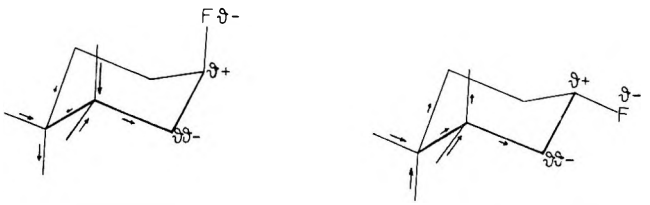


Figure 5. Electron flow generated by the linear electric field effect of point charges[1] (~0.3 electron units at C_α and X; 0.01 electron units at C_β).

5 is very similar to $\Delta\nu$ on C_2 and independent of X orientation. Linear electric field effects could play a minor role[1] since in **1a** one C–H bond of **1e**, which is gauche to C_α–X, is replaced by a more polarizable C–C bond. The estimated accumulation of electron density at C_β, however, is too small to account for the observed difference of 3–4 ppm. A steric origin of the β-shift difference is supported by the results of molecular mechanical calculations,[12b] which indicates rather consistent $C_\alpha C_\beta C_\gamma$ and $XC_\alpha C_\beta$ bond angle widening in axial-substituted cyclohexanes. Additional alkyl groups in the 3 or 4 positions to C_α (**2, 3, 5,** and **7**) or in the 3 position to the observed C_β (C_6 in **6**) exert negligible influence on β substituent effects ($\leq$0.5 ppm). Methyl groups in the 1 or 2 position (**4, 5,** and **6**) lead to similar β $\Delta\delta$ values attenuated by 1–3 ppm.

Anti γ Effects. Electronegative substituents of the second row, such as N, O, or F, are known to produce shielding at a γ carbon in antiperiplanar position.[20,30] The shielding is not substantially altered by additional equatorial alkyl groups (cf. **2, 3, 6,** and **7**), but replacement of the axial C_α–H bond by a C_α–C bond (**4** and **5**) leads to dramatic changes in sign and magnitude of $\Delta\nu$. This sign reversal is *not* limited to bridgehead compounds[22,30,31] but is in fact found in all tertiary derivatives as well as in carbocyclic systems,[22,32] where the axial hydrogen at C_γ is substituted by a C_γ–C bond. The anti γ deshielding by 2.5–4 ppm in these compounds can partially be assigned to linear electric field effects.[1]

The reversal of anti γ shielding effects in systems not containing the specific arrangement of syn axial C–H bonds at C_α and C_γ does not lend support to the suggestion[30] of a hyperconjugative charge transfer from X to C_γ. The alternating shifts at C_α, C_β, and C_γ have been related to the Pople–Gordon[33] charge alternation effect,[7d,34] but several observations, such as increasing β effects from X = F to X = I for example or the shift reversal cited above, are not explicable on this basis. Furthermore, MO calculated charge densities fail to reflect β and γ shifts (Figure 2). It can be shown,[12a] however, that very small electron density accumulations (<2%) at C_β will give rise to shielding electron flows in bonds at C_γ while the corresponding linear field effect at C_δ, generated by the C_α–X dipole, remains essentially unaffected (Figure 5).[35]

Syn γ Effects. Different mechanisms must be responsible for the pronounced shielding of γ carbons in gauche conformations **1a**. Sterically induced charge polarizations along C_γ–H bonds have been invoked for these effects in hydrocarbons.[12b,36] Clearly, the shielding exerted by substituents of small van der Waals radii like fluorine is of a different nature. Linear electric field effects, polarizing mainly the axial C_γ–H bond, correctly predict the sign, although not accurately the magnitude, of the observed shielding.[8,12a] Another factor is likely to result from n_X^*–σ_H overlap since the lone pair orbitals of heteroatom X are in close contact with the σ_{CH} orbitals of the axial C_γ–H bonds. The magnitude and sign of axial substituent induced shieldings on ring C_γ in cyclohexanes are remarkably independent of the presence of other alkyl groups (**2–7**). Notable exceptions are found in cyclohexane[37] and bicyclo[2.2.1]heptane[12,32] compounds, where *de*shielding substituent effects are observed due to the occurrence of axial C_γ–C instead of C_γ–H bonds. Sterically induced charge polarization also is predicted to lead to *de*shielding for certain conformational arrangements,[12b] particularly with sensor groups such as CH_3, which easily change torsional angles. Syn γ effects on methyl carbon shifts, as in **6**, are partially diminished, possibly as a result of widened torsional angles and subsequent smaller 1,4 interaction between γ-CH_3 and X.

Effects on C_δ and More Remote Carbon Atoms. Electronegative substituents invariably shield carbon δ by 1–2 ppm, axial groups in all cases to a significantly lesser degree. Additional alkyl substituents in various ring positions leave the X substituent effects constant to within ±0.3 ppm, unless special solvent susceptibilities are to be expected (as with cyclohexyl iodides) or unless bulkier substituents lead to distortions of the cyclohexane skeleton [see **6** (X = e-CH_3) and **2** (X = a-CH_3)]. δ effects in cyclohexanes bearing X and methyl groups alternatively in equatorial or axial positions (**3, 4, 6,** and **7** with axial X) are obscured if the conformer with the axial methyl cannot be measured separately in low temperature spectra. Since δ carbons are remote from direct interactions with the substituents, their shielding can be represented by linear electric field effects[12a] (Figure 5). Again, CNDO or INDO calculated charge densities fail to reproduce the C_δ shifts, while a frontier orbital treatment at least qualitatively[38] predicts an accumulation of electron density at C_δ by electronegative substituents at C_α.

As to be expected on the basis of linear electric field effects, C_ϵ and C_ζ in **2** are shielded by electronegative C_α substituents by less than 0.5 ppm. The differences for varying X groups are too small to warrant quantitative consideration. They shed light on long range substituent effects in steroids, where in specific cases long range effects above 1 ppm are observable, which must be due partially to conformational (steric) transmission.[39]

Conformational Equilibria. Methods. Valuable information on cyclohexane conformations has been obtained from ^{13}C NMR spectra, particularly of methyl and hydroxy derivatives at room temperature.[40] The advance of new techniques in dynamic NMR spectroscopy opens access to more quantitative measurements of equilibrium constants K. Possible pitfalls in the application of indirect methods, relying mostly on model compounds, have been aptly discussed elsewhere.[41] Time-averaged ^{13}C shifts can be used for the population analysis of rapidly equilibrating species, e.g., *n*-butane, if the temperature dependence of the shieldings is known,[42] but for the more slowly interconverting chair cyclohexane conformers, direct integration of separately visible NMR signals is clearly preferable.[41] The advantage of low temperature ^{13}C over ^1H NMR spectroscopy has been exploited already in several investigations[43–45] and can be seen in (i) the availability of several exchanging signal pairs, yielding 3–4 values for K and consequently numbers for the errors $\Delta\Delta G°$ as given in Tables V and VI, (ii) the wide spread of shift differences between exchanging signals, enhancing the observable temperature range, and (iii) the simplicity of the proton noise-decoupled spectra without additional isotopic substitution.

As with ^1H NMR spectroscopic signal integration,[41] the use of ^{13}C signal intensities requires some general precautions. Differences in T_1 relaxation times for stereoisomeric carbon atoms can lead to erroneous intensities in PFT accumulated spectra if relaxation is slower than pulse repetition. For this and other reasons (see Experimental Section), we have applied smaller pulse angles, which generate only minor distortions of the Boltzmann equilibrium.

That saturation effects do not affect the observed intensity ratios in cyclohexanes at 180 K (lifetime $\tau \sim 0.1$ s) was secured by an experiment applying pulse angles of 18, 35, and 90° (pulse delay 10 s) to a solution of cyclohexyl bromide in $CFCl_3$. Intensity ratios from all 4 carbon signals of 19.9, 20.5, and 19.8,

Table V. Free Energy Differences ($\Delta G°$) of Monosubstituted Cyclohexane Conformers[a]

X	registry no.	temp	^{13}C NMR–PFT $\Delta G°$	^{13}C NMR–PFT $\pm\Delta\Delta G°$	^{1}H NMR–PFT $\Delta G°$	^{1}H NMR–PFT $\Delta\Delta G°$	^{13}C NMR (ref 44a)[b]	^{1}H NMR (ref 41)[b]
F		180	0.360	0.025			0.38	0.270
Cl	542-18-7	180	0.507	0.04	0.539	0.055	0.53	0.52
Br	108-85-0	180	0.485	0.025	0.478	0.025	0.61	0.48
I	626-62-0	180	0.490	0.02			0.59	0.47
OH	108-93-0	193	1.01	0.03			1.01[40c]	0.97
OH		190	1.11[d]	0.04[d]				
OCH_3	931-56-6	180	0.750	0.035				0.56 (OCD_3)
OOCH		180	0.617	0.02	0.602	0.040		0.59
$OOCCH_3$	622-45-7	180	0.785	0.03	0.774	0.035		0.71
$OOCCF_3$	1549-45-7	180	0.575	0.02				0.54
$OOCC_6H_5$		180	0.500	0.022				
$OSiMe_3$		170	0.735	0.02				
OTs	953-91-3	190	0.475	0.035	0.409	0.033		0.52
OTs		190	0.445[d]	0.04[d]				
NH_2	108-91-8	193	1.23	0.03			1.45[c]	1.10
-NC		180	0.190	0.01				0.21
NCS		180	0.206	0.02				0.28
N_3		180	0.622	0.022	0.587	0.042		0.75
NO_2	1122-60-7	193	1.13	0.03			1.27[44b]	1.05
SH		193	1.22	0.04				1.20
-C≡CH		182	0.515	0.012				0.41
CN		178	0.214	0.02				0.24

[a] $G°$ is in kcal/mol; temperature is in K; 20% in $CFCl_3$ with 5% Me_4Si, if not otherwise noted. [b] Literature $\Delta G°$ values as indicated, if not noted otherwise. Conditions for ref 44a: 20–30% in CS_2 (RF with acetone and methanol) at 183–195 K. For ref 41: 20% in CS_2 at 190–200 K. [c] Reference 45b; $\Delta G°$ calculated from *cis*-4-methylcyclohexylamine. [d] CS_2.

Table VI. Free Energy Difference ($\Delta G°$) of Disubstituted Cyclohexane Conformers[a]

Y	registry no.	$\Delta G°$	$\pm\Delta\Delta G°$	$\Delta G°$(calcd)[b]
a-1-Cl	931-78-2	1.07	0.03	1.14
a-1-Br	931-77-1	1.19	0.03	1.17
a-1-OH	590-67-0	0.31	0.04	0.73
a-1-OH		0.335[e]	0.05[e]	
a-1-$OOCCH_3$	16737-30-7	0.775	0.04	0.85
a-2-OH		0.67	0.05	0.73
a-2-$OOCCH_3$		0.76	0.03	0.85
a-2-NH_2		0.57	0.03	0.51
a-3-OH[d]		>1.2		0.73
a-3-$OOCCH_3$[c]	66922-08-5	>1.2		0.85
a-3-NH_2		0.56	0.03	0.51
a-4-OH	7731-28-4	0.83	0.04	0.73
a-4-$OOCCH_3$	13332-20-2	0.93	0.02	0.85
a-4-NH_2	2523-56-0	0.62	0.03	0.51
a-4-*i*-$CHMe_2$[d]	6069-98-3	0.31	0.04	0.39

[a] See footnote a in Table V; 192 K unless noted otherwise; X = e-CH_3. [b] Calculated $\Delta G°$ assuming additivity (see text). [c] Estimated from line width near coalescence (see Experimental Section). [d] Isomenthane, at 183 K. [e] CS_2.

respectively, were observed, corresponding to $\Delta G° = 490 \pm 15$ cal/mol.

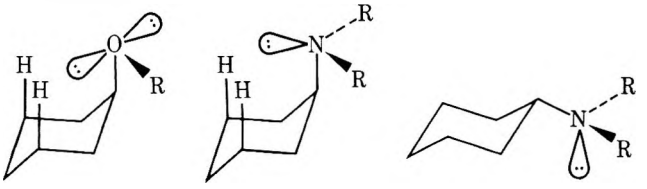
Under proton noise decoupling conditions, differential nuclear Overhauser effects will give rise to deviations of signal areas mainly if, in the case of nonquaternary carbon atoms, the distance between carbon and directly bonded hydrogen does not remain constant.[46] That these differences usually are negligible, if one compares exchanging stereoisomeric carbon atoms, is shown by the consistency of signal area ratios in topomers[7b] and in epimeric mixtures.[47] Here we find the accuracy of quantitative ^{13}C spectroscopy surpassing that of ^{1}H NMR methods. Small but consistent signal area deviations are found only for carbon atoms C_α, which alternatively bear equatorial or axial substituents.[7b,44a,47] Our observation of larger C_α peaks, in most cases by 5%, in **1e** and related compounds supports the interesting suggestion of elongated equatorial as compared to axial C–H bonds in cyclohexanes.[48]

Taking additional precautions for signal integration (see Experimental Section), one can obtain $\Delta G°$ values reproducible and accurate to $\Delta\Delta G° = 2$–35 cal/mol (Tables V and VI), which we believe to be influenced by systematic errors to a lesser degree than those obtained by previously available methods. Substantial deviations from $\Delta G°$ values obtained by other workers using low temperature ^{1}H or ^{13}C NMR signal integration (see Table V) are noted for compounds where the equilibrium is sensitive either to solvent or substrate concentration changes (as with cyclohexyl iodide) or to concentration dependent hydrogen bonding (as with hydroxy[49] and amino compounds).

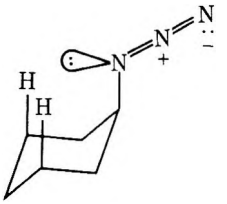
It has been noted that differential saturation can lead to weaker signals for the equatorial isomer in ^{1}H NMR–CW spectra.[41] That some resulting $\Delta G°$ values are indeed too small is supported by our and other[44] ^{13}C NMR values, which are consistently larger. In addition, we have reexamined some equilibria by ^{1}H NMR–PFT spectroscopy in the absence of saturation effects and find better agreement with $\Delta G°$ values determined by ^{13}C NMR spectroscopy (Table V).

Monosubstituted Cyclohexanes. Energies $\Delta G°$ of conformational equilibria should in principle be accessible by quantum mechanical calculations, but here they appear as very small differences between much larger ($\times 10^3$–10^5) total energies. More reliable information and insight into the different contributions to $\Delta G°$ can be expected from semiempirical molecular mechanical calculations, for which cyclohexane equilibria can provide important parametrization numbers. The free energy differences determined for halocyclohexanes by the improved NMR method (Table V and ref 44a) are in substantially better agreement with results from Allinger's extended force field[50] than are earlier values. An inspection of force field[12b,48] results for cyclohexanes suggests that the higher energy for axial halogen and methyl groups resides largely in bond angle distortions and in 1,3 diaxial repulsions, but only for X = a-CH_3 to a substantial degree in the gauche hydrogen interaction[48] of the equatorial hydrogen at C_1. This is the result of the particular outward bending of CH_3, which brings the corresponding equatorial hydrogen in strongly repulsive contact with the vicinal axial hydrogen atoms at C_2.

Conformational equilibria in cyclohexanes bearing substituents with lone electron pairs will largely depend on the either attractive[51–53] or repulsive interactions with the axial hydrogen atoms at C_γ. Earlier theoretical calculations suggested substantially smaller repulsions for nitrogen lone pairs as compared to hydrogen at intermediate distances (~3 Å).[53] For tropane compounds with 1,3 distances in the range of 2–3 Å, it could be shown recently by low temperature ^{13}C spectroscopy that the repulsive interactions of an *N*-methyl group are of comparable size to those in cyclohexanes, whereas very similar values are obtained for hydrogen and the lone electron pair at nitrogen.[54] Repulsive interaction between syn diaxial hydrogens at C_γ and lone electron pairs directed at them provides also rationalization of the decreasing destabilization of axial cyclohexyl oxygen derivatives with stronger electron-withdrawing substituents[41] (Table V; X = OCH_3, OMe_4Si, $OOCCH_3$, $OOCCF_3$, $OOCC_6H_5$, OTs). The lower electron density in the oxygen lone pairs is expected to lower the 1,3 repulsion if the rotamer with the substituent R at oxygen pointing away from the ring is dominant. That the rotamer distribution around the C_α–X bond is very similar for equatorial and axial oriented XY groups is supported by the indistinguishable shift of Y in compounds with Y = CH_3 or COR′ (X = O, N).



Substituents with multiple bonds in time-averaged $C_{\infty v}$ symmetry usually exert small repulsive interactions.[41] Their effective van der Waals radii are essentially determined by the electron densities in the outer orbitals.[55] The relatively large $\Delta G°$ value for X = –C≡CH is in excellent agreement with force field calculations[56] and reflects the high density at the carbon directly attached to the ring, which is substantially lowered in the nitrile derivative.[55] While the low $\Delta G°$ values for X = –NC and X = –NCS are understandable on the basis of absent lone electron pairs at N in the most important mesomeric form,[41,57,58] the corresponding azide must dominate in the form containing the lone pair at the N atom bonded at C_α.[57] In agreement with the observation on repulsive interactions between lone pairs at NR_2 or OR and the syn diaxial hydrogen atoms, this leads to the rather high destabilization for a-X = N_3 with $\Delta G°$ = 0.6 kcal/mol.[59]



Disubstituted Cyclohexanes. With the exception of dihalocyclohexanes, the conformational equilibria of polysubstituted rings have rarely been measured by direct NMR methods.[41] They can provide $\Delta G°$ values for groups which shift the equilibrium too much to the **1e** side in monosubstituted cyclohexanes to be measurable, provided one can neglect interactions between the substituents. Distortions transmitted by ring deformations will in addition be recognizable by deviations from additivity of $\Delta G°$ values. These distortions will be minimized in cis 1,4-disubstituted cyclohexanes, such as in isomenthane (**3**; X = $CH(CH_3)_2$). Assuming additivity, one obtains $\Delta G°$ = 2.1 kcal/mol for the isopropyl group; the difference from the methyl group value (1.74 kcal/mol[45a]) is believed to originate in the entropy disadvantage for the branched alkyl group.[60]

Since the investigated cyclohexanes contain only one polar bond besides alkyl groups, it is not unexpected that the observed equilibria show generally minor deviations from values expected on the basis of single $\Delta G°$ values (Table VI). Exceptions are noted particularly for alcohols and amines, in which the OH and NH_2 $\Delta G°$ constants are altered by self association.

Experimental Section

^{13}C and ^1H NMR spectra at low temperature were recorded in PFT mode at 22.62 (21.14 kG) and 90 MHz, respectively, on a Bruker HX 90/Nicolet 1080 system using $CFCl_3$ for ^{19}F field-frequency lock and Me_4Si as an internal standard. The temperature was controlled with a Bruker BST 100/700 unit and found to be accurate to ±0.5 K using a "chemical shift" thermometric system.[61] Spectral width was 6000 Hz for ^{13}C NMR and 900 Hz for ^1H NMR, both at 8K/4K data points. Pulse angles of 30° (^{13}C NMR) could be used without additional delay after the FID scan (0.6 s). This procedure lead in ~1 M solutions to sufficient signal/noise ratios (>50) after 10 min accumulation time and was found to be more economical than applying 90° angles,[44a] while no differential T_1 effects were observable. Digitization errors were minimized by using peak widths extending over several computer addresses. This was achieved by staying in the region of not too slow of exchange or by measuring under nonoptimal field homogeneity.

Signal area ratios were determined by cutting and weighing paper copies and additionally in several cases by electronic integration or by complete line shape simulation. Overestimation of the larger peak, yielding too high of $\Delta G°$ values, can result from the neglect of the valley signal height between exchanging peaks. This systematical error, which increases with $\Delta G°$, must be minimized by the choice of not too fast of exchange or by line shape analysis and requires high signal to noise ratios. The accuracy obtainable is given in Tables V and VI; the reproducibility was checked with freshly prepared solutions of **1** (X = I, NCS, and OTs), yielding $\Delta\Delta G°$ deviations of 0.02, 0.002, and 0.012 kcal/mol, respectively.

Isomers of less than 5%, e.g., **7** (X = a-OH, a-OAc), were determined from the line shape at intermediate exchange rates. Since both $\Delta\nu$ and the exchange rate can be estimated from other cyclohexanes, the population is unambiguously deducible from the observed line shapes. In a typical experiment, 1% of the minor isomer produces for $\Delta\nu$ = 100 Hz and $k = 10^3\ s^{-1}$ an exchange broadening of 1.5 Hz at the "coalescence" point.

The preparation of materials that are not commercially available will be reported elsewhere.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Professor M. Ashworth for help with the manuscript preparation.

Registry No.—Methanesulfuric acid cyclohexyl ester, 66922-09-6; *N*-methylcyclohexylamine, 100-60-7; *N,N*-dimethylcyclohexylamine, 98-94-2; *N*-carboxaldehydecyclohexylamine, 766-93-8; cyclohexa-

necarboxyaldehyde, 2043-61-0; benzoylcyclohexane, 712-50-5; cyclohexanecarboxylic acid ethyl ester, 3289-28-9; cyclohexanemethanol, 100-49-2; *trans*-1-chloro-4-methylcyclohexane, 13064-82-9; *cis*-1-chloro-4-methylcyclohexane, 13064-81-8; *trans*-1-bromo-4-methylcyclohexane, 28046-91-5; *cis*-1-bromo-4-methylcyclohexane, 28046-90-4; *trans*-1-iodo-4-methylcyclohexane, 66922-10-9; *cis*-1-iodo-4-methylcyclohexane, 66922-11-0; *trans*-1-hydroxy-4-methylcyclohexane, 7731-29-5; *trans*-1-amino-4-methylcyclohexane, 2523-55-9; *trans*-1,4-dimethylcyclohexane, 2207-04-7; *cis*-1,4-dimethylcyclohexane, 624-29-3; methylcyclohexane, 108-87-2; 1-fluoro-1-methycyclohexane, 66922-12-1; 1-iodo-1-methycyclohexane, 40304-83-4; 1,1-dimethycyclohexane, 590-66-9.

Supplementary Material Available: ^{13}C NMR shifts of cyclohexane derivatives which are not reported in Tables I–IV (Tables Ia, Ib, and IIa) and Figure 6 (experimental and calculated line shape; example for possible error by valley signal height neglect) (6 pages). Ordering information is given on any current masthead page.

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Steric and Conformational Effects in the Solvolysis of Ring-Fused Tertiary Cyclopropyl Derivatives

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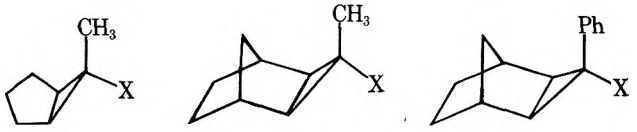
3-Methyl-*exo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl tosylate (**2**-OTs) and the methyl-d_3 analogue (**2**-OTs-d_3) have been prepared along with 3-phenyl-*exo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl trifluoroacetate (**3**-OTFA). Acetolysis of these substances gave only allylic acetates. Rate data suggest considerable steric rate enhancements for both **2**-OTs and **3**-OTFA. The β-deuterium isotope effect in the solvolysis of **2**-OTs was 1.33 ± 0.02, a value considered quite small in view of the large ($10^{8.42}$) α-methyl/α-hydrogen rate ratio. This was interpreted in terms of a sterically induced unfavorable transition-state conformation necessary for maximal hyperconjugative stabilization in the incipient cyclopropyl cation. Solvolysis of 1-phenylcyclopropyl derivatives was used as a model for the unassisted, k_c, formation of the 1-phenylcyclopropyl cation. Comparison of rate data with that of **3**-OTFA gave a steric rate enhancement for phenyl which was comparable to that of a methyl group. Conformational factors were suggested to account for a decreased phenyl steric effect.

The solvolysis of cyclopropyl substrates has been an area of continuing interest.[2] Our interest in this area has led us to construct systems in which incipient cyclopropyl cation centers interact with adjacent olefinic centers.[3,4] We have also found that concerted ionization–electrocyclic opening to an allylic cation can be prevented by fusion of an *endo*-norbornyl system to a secondary cyclopropyl triflate.[3] Similarly the tertiary cyclopropyl system **1**, with the cyclopentyl ring fused to the cyclopropyl system and a leaving group in the exo po-

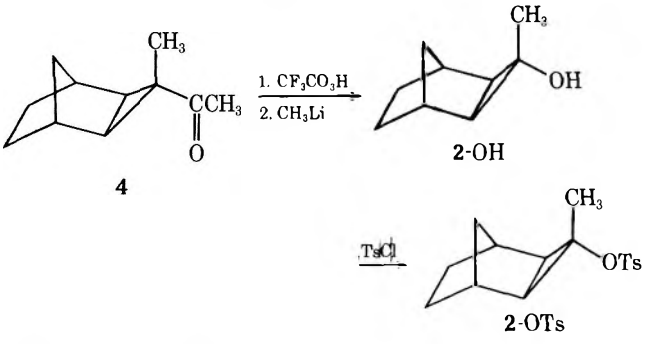


1 **2** **3**

sition, undergoes stepwise processes giving a cyclopropyl cation, followed by rearrangement to an allylic cation.[5] The β-deuterium isotope effect in the solvolysis of **1** (X = OTf) was 1.42, a value not inconsistent with such a mechanism.[6] The importance of steric effects in the ionization of **1** was an unknown factor. We were therefore interested in preparing the tricyclo[3.2.1.$0^{2,4}$]octyl systems **2** and **3** in order to evaluate the importance of steric effects in the ionization of these systems. We also wanted to evaluate the β-deuterium isotope effect in the ionization of **2** in view of the large demand for hyoerconjugative stabilization in the cyclopropyl cation and the expected large steric interaction of the methyl group with the C-8 methylene group. We report here the results of studies on cyclopropyl systems **2** and **3**.

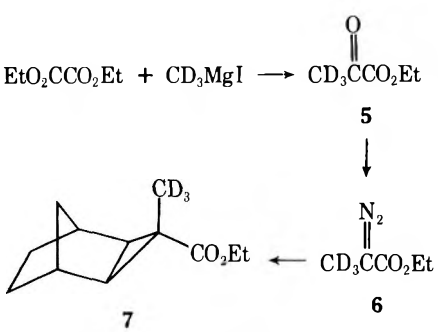
Results

Preparation and Acetolysis of 2-OTs. Our synthetic approach to the preparation of derivatives of **2** involved the



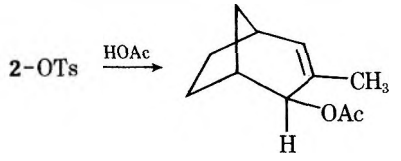
4 **2-OH** **2-OTs**

addition of methylcarboethoxycarbene to norbornene as previously described.[7] Further transformations previously described allowed the preparation of ketone **4**.[7] Baeyer–Villiger oxidation gave the corresponding acetate[8] which was converted to alcohol **2**-OH and tosylate 2-OTs. The preparation of the deuterated tosylate, **2**-OTs-d_3, required the preparation of ethyl diazopropionate-d_3, (**6**). Treatment of diethyl oxalate with methylmagnesium-d_3 iodide gave ethyl pyruvate-d_3 **5** which was converted to **6** via pyrolysis of the tosylhydrazone salt. Photosensitized addition of **6** to norbornene gave **7** which led subsequently to the preparation of **2**-OTs-d_3.



7 **6**

Solvolysis of **2**-OTs in acetic acid gave allylic acetate **8** as



8

the sole product. Kinetic data are also given in Table I. The β-deuterium isotope effect in **2** determined from the data in Table I is 1.33 ± 0.02. Comparison with 1-OTs shows that **2**-OTs is 2.4 × 10^3 more reactive in acetic acid at 50 °C.

Preparation and Acetolysis of 3. The synthetic entry into the phenyl-substituted system, **3**, is shown below. Addition of phenylcarbene to norbornene gave a mixture of hydrocarbons **9** and **10**. Treatment of this mixture with butyllithium–TMEDA followed by oxygen led to alcohol **3**-OH. The exo isomer **10** does not react under these conditions and only the exo alcohol **3**-OH is formed. The tosylate derivative of **3**-OH was expected to be too reactive for convenient preparation and solvolysis. The *p*-nitrobenzoate derivative was expected to require an extremely high temperature to induce solvolysis. The trifluoroacetate derivative, **3**-OTFA, was therefore prepared since this derivative was expected to have intermediate reactivity.

Solvolysis of **3**-OTFA in acetic acid gave allylic acetate **11** as the sole product. Kinetic data are also given in Table I along with data for phenylcyclopropyl trifluroacetate (**12**), for comparison. Acetolysis of **3**-OTFA is 1.3 × 10^3 faster than **12**.

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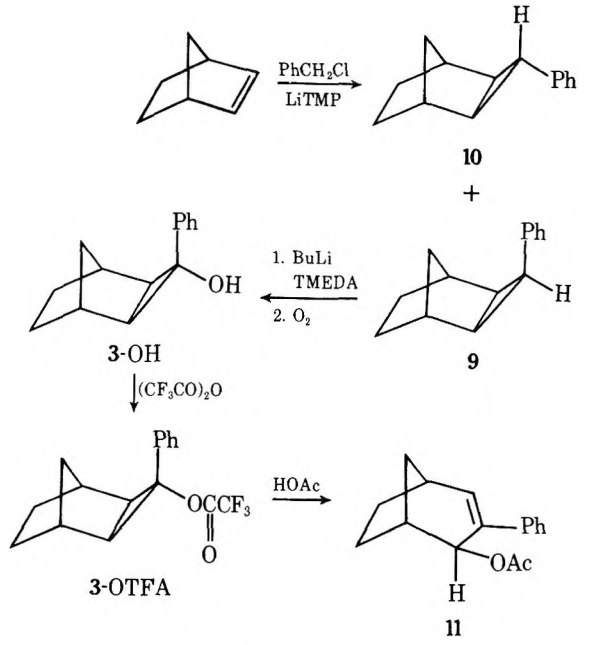
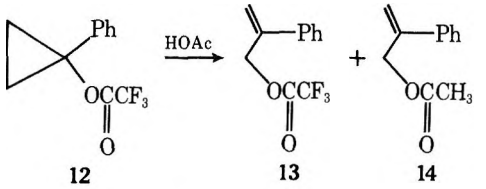


Phenyl trifluoroacetate **12** gives mostly a product of internal return, allylic trifluoroacetate **13** along with about 20% allylic acetate **14** at low conversion of **12**. At higher conversion of **12**, concommitent solvolysis of **13** produces more of the allylic acetate **14**. These results parallel those of DePuy[9] in the solvolysis of phenylcyclopropyl tosylate.



Discussion

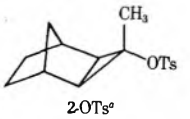
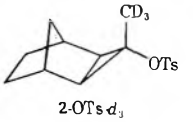
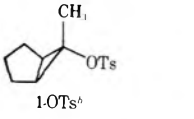
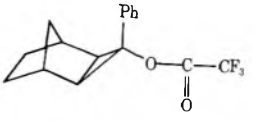
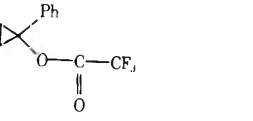
The solvolysis of **2**-OTs is best explained in terms of stepwise formation of a tertiary cyclopropyl cation, **15**, followed by opening to an allylic cation **16** and solvent capture. Similar behavior is seen in the solvolysis of **1**.[5] Initially apparent is the large rate enhancement in the acetolysis of **2**-OTs. A comparison with 1-OTs shows a rate enhancement of 2.4×10^3. This is attributed to relief of ground state strain, due to an unfavorable methyl–C_8 interaction in **2**. Rate enhancement due to relief of ground state strain (B strain) is a well-documented phenomenon.[10] The actual magnitude of the steric rate acceleration in **2**-OTs is difficult to assess since steric effects could also be important in the solvolysis of 1-OTs.

Considering the observed steric rate enhancement in **2**-OTs, the β-deuterium isotope effect is quite interesting. The value of 1.33 must be considered quite small in view of the large demand for hyperconjugative stabilization in the unstable cyclopropyl cation. The β-deuterium isotope effect in 1-OTf[6] is 1.42, a value also considered relatively small. Any steric isotope effects[11] generated by steric crowding in **2**-OTs are not demonstrated in the measured isotope effect of only 1.33.

Servis, Borčić, and Sunko[12] have developed a correlation between the β-deuterium isotope effect and the α-methyl/α-hydrogen rate ratio. The α-methyl/α-hydrogen rate ratio for **2**-OTs is $10^{8.42}$, one of the largest yet determined[13] and indicative of a large demand for hyperconjugative stabilization.[12] The Servis, Borčić, Sunko (SBS) relationship predicts a β effect of 1.48, a value much larger than the observed value of 1.33. The conclusion based on the SBS relationship and comparison to the value for 1-OTf is that the β-deuterium isotope effect for **2**-OTs is unusually small.

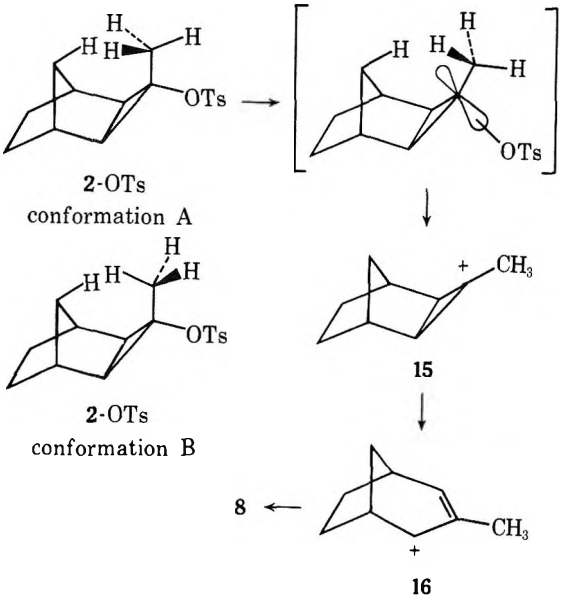
Examination of the possible methyl group conformations

Table I. Solvolysis Rates in Acetic Acid–0.1 M NaOAc

compd	registry no.	T, °C	$10^5 k$, s^{-1}
 2-OTs[a]	42856-12-2	70.0 50.0	54.3 5.48 ± 0.06
 2-OTs-d_3	66966-32-3	50.0	4.13 ± 0.00
 1-OTs[b]	66966-33-4	130.0 110.0 50.0[e]	26.3 3.65 2.28×10^{-3}
 3-OTFA[c]	66966-34-5	100.0 80.0	33.8 3.58
 12[d]	66966-35-6	160.0 142.0 100.0[e]	14.7 2.66 2.61×10^{-2}

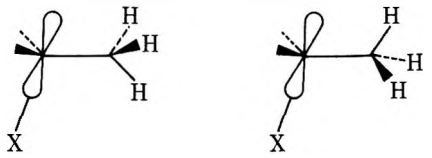
[a] $\Delta H^{\ddagger} = 24.6$ kcal, $\Delta S^{\ddagger} = -2$ eu. [b] $\Delta H^{\ddagger} = 29.6$ kcal, $\Delta S^{\ddagger} = -2$ eu. [c] $\Delta H^{\ddagger} = 29.9$ kcal, $\Delta S^{\ddagger} = 5$ eu. [d] $\Delta H^{\ddagger} = 33.1$ kcal, $\Delta S^{\ddagger} = 0$ eu. [e] Extrapolated value.

in **2**-OTs suggests a reason for this small isotope effect. It is suggested that conformation A is the preferred conformation of **2**-OTs, rather than conformation B in which there is a very unfavorable interaction with the C-8 proton. The hyperconjugative stabilization in the transition state derived from conformation A should be less than in the transition state derived from conformation B. A 0° dihedral angle between the developing p orbital and the adjacent proton, as in B, should



be preferred to the 60° angle in A for the observation of maximum isotope effects.[15] Similar arguments have been used by Shiner[16] to explain decreased isotope effects in conformationally rigid systems. While we do not suggest that **2**-OTs is held rigidly in conformation A, we do suggest that there is some barrier to attainment of a 0° dihedral angle in the transition state. This could account for the smaller than

normal isotope effect as seen in the solvolysis of 2-OTs. Hyperconjugative stabilization in the cationic intermediate de-

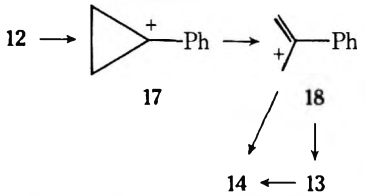


A B

rived from A should be the same as from B, but transition state stabilizations should differ.

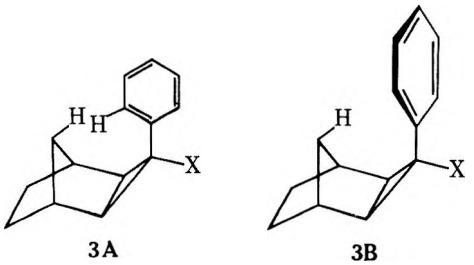
An alternative rationalization for the decreased isotope effect (suggested by a referee) involves the greater ability of 2-OTs-d_3 to populate conformation B due to the lesser steric demand in this substrate with solvolysis occurring preferentially from conformation B. While either of these two rationalizations would explain the reduced isotope effect, it appears clear that the effect is steric in origin.

Solvolysis of 3-OTFA can also be interpreted in terms of stepwise processes leading to a phenyl-substituted cyclopropyl cation and an allylic cation, respectively. Data for 1-phenylcyclopropyl trifluoroacetate (12) can be used to estimate the importance of steric acceleration in the acetolysis of 3-OTFA. We feel that solvolysis of 12 is a good model for the *unassisted* (k_c) stepwise formation of a 1-phenylcyclopropyl cation for the following reasons. It is not unreasonable to expect that the phenyl group could offset *all* of the participation due to concerted C_2–C_3 bond fragmentation during ionization of 12 in



view of the fact that a methyl group has been found to offset most of such participation in solvolysis of 1-methycyclopropyl triflate.[5] Additionally Brown has recently determined a ρ value for solvolysis of substituted phenylcyclopropyl dinitrobenzoates.[2] This rate data, along with DePuy's earlier data[9] indicate *no* abrupt change from a σ participation to a nonparticipating mechanism over a substituent range from *p*-methoxy to *p*-trifluoromethyl.[16] This is despite the fact that the *p*-methoxyphenyl derivative gives mostly ring retained products while the less activated substrates give solely allylic solvolysis products. This supports the stepwise mechanism over the entire aromatic substituent range despite the observation of only allylic products from 12. Finally, more direct evidence for the intermediacy of the 1-phenylcyclopropyl cation is its capture by borohydride in the solvolysis of 1-phenylcyclopropyl tosylate in aqueous diglyme.[5]

With these facts in mind, the steric enhancement in solvolysis rate of 3-OTFA is apparent. What is surprising is the fact that the magnitude (only a factor of 10^3) is less than steric acceleration in 2-OTs. Conformational effects again suggest a reason for this unexpected behavior. The "normal" conformation of a phenyl group bonded directly to a cyclopropane is as shown in **3A**.[18,19b] Due to an unfavorable steric interaction with the C-8 hydrogen, this conformation is unstable



3A 3B

relative to **3B**. It is not unreasonable to expect that a phenyl group held in conformation **3B** is less sterically demanding than the methyl group in **2**.

The NMR spectra of **9**, 3-OH, and 3-OTFA support the suggested conformation of **3B**. The aromatic region of **9** appears essentially as a singlet while that of **10** is complex. Closs[19] has discussed the reasons for this behavior in terms of phenyl conformations and anisotropic effects of the cyclopropane ring. This reasoning also supports **3B** as the preferred conformation of **9**. Additionally the syn C-8 protons in **9**, 3-OH, and 3-OTFA are shifted upfield, to δ 0.40, 0.37, and 0.40, respectively, due to the shielding effect of the aromatic ring in conformation **3B**. The corresponding syn C-8 proton of **10** appears at δ 1.20. The conclusion is that the preferred conformation of 3-OTFA is as in **3B** and that steric effects of the phenyl group in this conformation do not surpass those of the methyl group in 2-OTs.

In summary, this work shows the importance of steric effects in the ionization of tertiary cyclopropyl systems **2** and **3** as well as the importance of transition state conformation of a methyl group in determining β-deuterium isotope effects in **2**. The magnitudes of these steric effects are contrary to what is expected based on conformationally determined A values[20] of Taft E_s values[21] for phenyl vs. methyl.

Experimental Section

General. Gas chromatographic analyses were carried out on a Hewlett Packard Model 5750 using a 5 ft 5% SE 30 on Chromosorb G column. NMR spectra were recorded on a Varian A60A or a Varian XL-100 spectrometer in the Fourier transform mode and are reported vs. tetramethylsilane. Mass spectra were recorded on an AE1 Scientific Apparatus MS902 spectrometer.

Preparation of 2-OH. A solution of peroxytrifluoroacetic acid prepared from 811 mg of 90% hydrogen peroxide and 5.36 g of trifluoroacetic anhydride in 30 mL of methylene chloride was added slowly dropwise to a stirred solution of 1.25 g of ketone 4[7] in 40 mL of methylene chloride containing 25 g of dibasic potassium phosphate. After completion of the addition the mixture was refluxed for 1.5 h. The entire solution was then taken up into ether and water, washed with sodium carbonate solution, and dried over sodium sulfate. Solvents were removed by distillation through a Vigreux column and the residue was distilled to give 1.03 g (75%) of previously reported *endo*-3-methyl-*exo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl acetate,[8] bp 60–63 °C (0.52 mm): NMR (CCl_4) δ 2.44 (2 H, m), 1.84 (3 H, s), 1.53 (3 H, s), 1.50–0.50 (8 H, m).

A solution of 0.88 g of the acetate obtained above in 7 mL of ether was cooled to 0 °C and 6.8 mL of 1.84 M methyllithium was added dropwise. After completion of the addition, the solution was cooled to −78 °C and 0.65 g of acetic acid in 5 mL of ether was added. After warming to approximately 10 °C, the organic phase was separated, washed with water and saturated sodium chloride solution, and dried over sodium sulfate. Solvent was removed on a rotary evaporator with the last traces being removed by vacuum pump. The yield of crude previously reported[8] alcohol 2-OH was 0.55 g (82%). Alcohol 2-OH was relatively unstable with respect to rearrangement to 2-acetylnorbornane.

Preparation of 2-OTs. A solution of 750 mg of *p*-toluenesulfonyl chloride in 5 mL of pyridine was cooled to 0 °C and 0.55 g of alcohol 2-OH was added. The solution was stored in a refrigerator for 29 h and an aqueous workup followed. Pyridine was removed by washing with cold, dilute hydrochloric acid. After drying the organic extract over anhydrous sodium sulfate, the solvent was removed by a rotary evaporator. The residue, which crystallized on cooling, was slurried with cold pentane and the solid (415 mg, 36%, mp 44–46 °C) was collected and washed with pentane: NMR (CCl_4) δ 7.85–7.15 (4 H, AA′BB′ quartet), 2.45 (3 H, s), 1.72 (3 H, s), 1.55–1.10 (7 H, m), 0.74 (1 H, broad d, J = 11 Hz). Traces of unreacted *p*-toluenesulfonyl chloride in 2-OTs produced in certain runs were found to interfere with accurate determination of rate constants. To avoid this problem, the crude tosylate in pyridine was treated with a small amount of aqueous potassium hydroxide solution to remove the unreacted *p*-toluenesulfonyl chloride before crystallization.

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.90; H, 7.09.

Preparation of Ethyl Pyruvate-d_3 (5). Methylmagnesium-d_3 iodide was prepared from 25 g of methyl iodide (Aldrich Chemical Co.)

and 5.13 g of magnesium in 100-d_3 mL of ether. The Grignard reagent was added dropwise over a 2.5-h period to a solution of 68.8 g of diethyl oxalate in 140 mL of ether held at −78 °C. After completion of the addition, the mixture was warmed to 0 °C and then decomposed with ammonium chloride solution. The organic phase was separated and dried over sodium sulfate. Solvent was removed by distillation through a Vigreux column and the residue was distilled through a column packed with glass helices at 100 mm. The fraction boiling at 88–93 °C (9.49 g, 46%) was ethyl pyruvate-d_3 (**5**). NMR analysis shows no signal at δ 1.95 due to undeuterated ethyl pyruvate. A higher boiling fraction (115 °C) consisting of unreacted diethyl oxalate could also be collected.

Preparation of 2-OTs-d_3. The preparation of ethyl diazopropionate-d_3 (**6**) was accomplished by vacuum pyrolysis of the sodium salt of the tosylhydrazone of **5** as previously described for preparation of undeuterated ethyl diazopropionate. The addition of **6** to norbornene was as previously described for the undeuterated ethyl diazopropionate.[22] The remainder of the sequence for the preparation of **2**-OTs-d_3 was completely analogous to the preparation of **2**-OTs. The NMR spectrum of **2**-OTs-d_3 showed no signal at δ 1.72.

Reaction of Norbornene with Benzyl Chloride and LiTMP. A solution of LiTMP[23] prepared from 17.5 mL of 1.84 M methyllithium and 5.02 g of tetramethylpiperidine in 4 mL of ether was added dropwise to a solution of 3.46 g of benzyl chloride and 19.9 g of norbornene in 8 mL of ether at −10 °C over a 1-h period. After completion of the addition, the mixture was warmed to room temperature and stirring was continued for 3.2 h. The mixture was quenched with water and the organic phase was separated and washed with dilute hydrochloric acid until the aqueous phase remained acidic. After washing with saturated sodium chloride solution and drying over sodium sulfate, the solvent and norbornene were removed by distillation through a Vigreux column at atmospheric pressure. The residue was distilled through a short path condenser and collected in two fractions. Fraction 1, bp 62–69 °C (0.04 mm), weighed 0.96 g and was enriched in the *endo*-phenyl isomer **9**. Fraction 2, bp 69–95 °C (0.04 mm), weighed 0.96 g and was enriched in the *exo*-phenyl isomer **10**. The total yield of **9** and **10** was 1.92 g (38%). A previous run showed a 1.2 to 1 ratio of 9:10 as determined by gas chromatography. Samples of each product were isolated by preparative gas chromatography. NMR of **9** (CCl_4) δ 7.17 (5 H, bs), 2.40 (2 H, m), 1.78 (1 H, t, J = 7.5 Hz), 1.36 (4 H, m), 1.11 (2 H, d, J = 7.5 Hz), 0.40 (2 H, m); mass spectroscopic molecular weight 184.1254 (calcd. for $C_{14}H_{16}$, 184.1252). NMR of **10** (CCl_4) δ 7.3–6.7 (5 H, m), 2.42 (2 H, m), 1.77 (1 H, t, J = 3 Hz), 1.40 (4 H, m), 1.20 (1 H, br d, J = 11 Hz), 0.98 (2 H, d, J = 3 Hz), 0.75 (1 H, br d, J = 11 Hz); mass spectroscopic molecular weight 184.1254 (calcd. for $C_{14}H_{16}$, 184.1252).

Preparation of 3-OH. A mixture of phenylcyclopropanes **9** and **10** (0.96 g of the first fraction previously described) was added to a solution of 3.25 mL of 2.4 M *n*-butyllithium in hexane containing 1.01 g of tetramethylethylenediamine and 3 mL of ether at 0 °C. The solution turned light red upon addition of the mixture of **9** and **10**. The solution was then stirred at room temperature for 1 h after which time the solution was a deep red color. The mixture was then cooled to −35 °C and the flask was equipped with a gas bubbler. Oxygen was continuously added at this temperature for 40 min. The red color had significantly faded. The mixture was warmed to −20 °C and 0.97 g of acetic acid was added to the reaction mixture. Water was then added and the organic phase was separated, washed with water and saturated sodium chloride solution, and dried over sodium sulfate. The solvent was removed by rotary evaporation. Crystals of **3**-OH formed on removal of the solvent. The residue was slurried in cold pentane and the solid was collected to give 0.17 g of **3**-OH: mp 146–146.5 °C; NMR (CCl_4) δ 7.30 (5 H, br s), 2.33 (2 H, m), 1.47 (1 H, s, exchange with D_2O), 1.38 (4 H, br s), 1.24 (2 H, s), 0.37 (2 H, m); mass spectroscopic molecular weight, 200.1276 (calcd. for $C_{14}H_{16}O$, 200.1201).

Preparation of 3-OTFA. A solution of 140 mg of trifluoroacetic anhydride in 1.5 mL of pyridine was cooled to 0 °C and 81 mg of **3**-OH was added. The mixture was stored in a refrigerator overnight. After an aqueous workup with ether extraction, pyridine was removed by washing the organic phase with dilute hydrochloric acid. The organic phase was dried over sodium sulfate and the solvent was removed by distillation through a Vigreux column. The residue was distilled to give 81 mg (67%) of **3**-OTFA, bp 60–65 °C (0.04 mm). Gas chromatographic analysis showed a single product. On storage in a refrigerator, **3**-OTFA crystallized: mp 50–51 °C; NMR ($CDCl_3$) δ 7.60–7.20 (5 H, m), 2.52 (2 H, br s), 1.58 (4 H, br s), 1.41 (2 H, br s), 0.40 (2 H, br s); mass spectroscopic molecular weight 296.1064 (calcd. for $C_{16}H_{15}F_3O_2$, 296.1024).

Preparation of 1-Phenylcyclopropyl Trifluoroacetate (12). A solution of 4.7 g of trifluoroacetic anhydride in 15 mL of pyridine was cooled to 0 °C and 2.00 g of 1-phenylcyclopropanol[24] was added. After 3.5 h at 10 °C, an aqueous workup followed. The product was isolated by distillation giving 3.06 g (89%) of **12**: bp 56–58 °C (1.6 mm); NMR (CCl_4) δ 8.60–8.18 (5 H, m), 1.50–1.20 (4 H, m); mass spectroscopic molecular weight 230.0553 (calcd. for $C_{11}H_9F_3O_2$, 230.0555).

Solvolysis of 1-OTs and 2-OTs. Kinetic Method. The kinetic procedure for solvolysis of tosylates involved the titrimetric method already described.[3]

Solvolysis of 3-OTFA. Kinetic Method. Solvolysis rates of **3**-OTFA were measured using the sealed tube method and were monitored by ultraviolet spectroscopy by observing the appearance of the styrene chomophore at 250 nm. At given time intervals, 1-mL aliquots of a solution of **3**-OTFA in acetic acid were diluted to 25 mL with methanol and the absorbance at 250 nm was recorded. Rate constants were calculated by the usual method and agreed well with rates estimated by gas chromatographic analysis.

Solvolysis of 1-Phenylcyclopropyl Trifluoroacetate (12). Kinetics Method. Solvolysis of **12** was done using the sealed tube method and was monitored by gas chromatography using biphenyl as an internal standard. At given time intervals, 1-mL aliquots of a solution of **12** in acetic acid were diluted with 2.5 mL of ether. Extractions were done with 2.5 mL of water, 3.0 mL of water, and 1.0 mL of Na_2CO solution, respectively. A solution of biphenyl (1.0 mL) prepared from 0.451 g in 25 mL of ether was added followed by Na_2SO_4. The solutions were then analyzed for remaining **12** by gas chromatography at 100 °C. Rate constants were calculated in the usual manner by the least-squares method and had minimum correlation coefficients of 0.9996.

Solvolysis of 2-OTs, 3-OTFA, and 12. Product Analyses. A sample of substrate in acetic acid–0.1 M NaOAc was heated (sealed tube) for 10 half-lives. Trifluoroacetate **12** was only heated for 2 half-lives. An aqueous workup followed. Gas chromatographic analysis of the products from **2**-OTs and **3**-OTFA showed single products, **8** and **11**, respectively. Similar analysis of the solvolysis of **12** showed the presence of **13** and **14**. Samples of all products were isolated by preparative gas chromatography and structures were confirmed by NMR and infrared and mass spectroscopy. NMR of **8** ($CDCl_3$) δ 5.88 (1 H, doublet of quartets, J = 7, 1.5 Hz), 4.80 (1 H, d, J = 3 Hz), 2.46 (2 H, m), 2.07 (3 H, s), 1.95–1.08 (9 H, m with doublet, J = 1.5 Hz at 1.58); mass spectroscopic molecular weight 180.1165 (calcd. for $C_{11}H_{16}O_2$, 180.1150). NMR of **11** ($CDCl_3$) δ 7.3 (5 H, m), 6.57 (1 H, d, J = 7 Hz), 5.60 (1 H, d, J = 3 Hz), 2.88–2.48 (2 H, m), 1.96 (3 H, s), 1.86–1.18 (6 H, m); mass spectroscopic molecular weight 242.1293 (calcd. for $C_{16}H_{18}O_2$, 242.1307). NMR of **13**[9] ($CDCl_3$) δ 7.42 (5 H, bs), 5.67 (1 H, s), 5.47 (1 H, s), 5.25 (2 H, s). NMR of **14** ($CDCl_3$) δ 7.6–7.2 (5 H, m), 5.58 (1 H, bs), 5.40 (1 H, bs), 2.08 (3 H, s).

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Registry No.—**2**-OH, 66966-36-7; **3**-OH, 66966-37-8; **4**, 42856-10-0; **5**, 66966-38-9; **8**, 66966-39-0; **9**, 67010-34-8; **10**, 66966-40-3; **11**, 66966-41-4; **13**, 66966-42-5; **14**, 7534-40-9; *endo*-3-methyl-*exo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl acetate, 67010-35-9; MeI-d_3, 865-50-9; diethyl oxalate, 95-92-1; benzyl chloride, 100-44-7; norbornene, 498-66-8; 1-phenylcyclopropanol, 29526-96-3.

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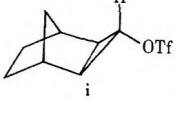

i

for i at 50 °C[14] and a triflate:tosylate rate ratio of $10^{4.78}$. This is the measured rate ratio of 1-OTf/1-OTs at 50 °C. See ref 5 and 14 and Table I.
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Steric Relief Control of Solvolysis Rates of 1-Alkyl-2-adamantyl Substrates. Empirical Force-Field Calculations

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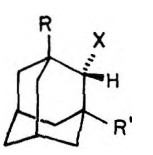
8-Cyano-4-*exo*-protoadamantanol (*exo*-**3**) isolated from the solvolysis of 1-cyano-2-adamantyl tresylate (**1g**-OTres) was oxidized to 8-cyano-4-protoadamantanone (**4**), which was reduced by sodium borohydride to a 5:4 mixture of 8-cyano-4-*endo*-protoadamantanol (*endo*-**3**) and *exo*-**3**. No *endo*-**3** was evidenced in the original solvolysis mixture from **1g**-OTres, so that solvolysis of **1g**-OTres is as stereoselective as the solvolysis of the 1-methyl analogue (**1b**-OTs). The variation of steric strain in the ionization of 1-alkyl-2-adamantyl substrates (**1b–e**) was evaluated by force-field calculations. A significant relief of steric strain [Δ(strain)] was found for this process, and it was correlated with the rates of solvolysis (k) by the equation: $\log k = 0.63\Delta(\text{strain}) - 6.73$ ($r = 0.9693$, SD = 0.271). Thus, the rate increase produced by 1-alkyl substituents in the solvolysis of 2-adamantyl substrates is fully accounted for by the steric strain relief (which can be adjusted for a more refined treatment by a smaller polar effect of 1-substituents), and no other mechanistic assumption is necessary.

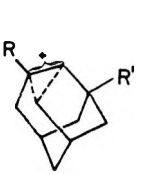
Empirical force field calculations[1] have been used to solve various problems in physical organic chemistry.[2] Recent applications permitted estimation of the most stable conformations of known[3] or as yet unsynthesized compounds;[4] calculation of barriers and pathways for conformer interconversions;[5] determination of the most stable member of a (usually large) family of isomeric hydrocarbons;[6] predictions or rationalizations of pathways in carbocationic isomerizations;[6a,7] and hydrogenolysis reactions of strained polycycles.[8] Examples of rationalization of products obtained in cyclizations[9] and in ring enlargements of carbocations[10] can also be noted. A special group of applications consists of the calculations of steric strain variations in reactions involving a change of hybridization at the reaction center and the correlation of reaction rates with the variations in strain energy. Thus, ester hydrolysis[11] and oxidation of secondary alcohols[12] were successfully correlated. The most useful results, however, were obtained for the solvolytic reactions involving carbocations by Schleyer, who pioneered the use of force field calculations for mechanistic studies of chemical reactions.[13]

It is the purpose of this paper to report on the application of this approach to the solvolysis of 1-alkyl-2-adamantyl substrates and to present new experiments in the study of the 1-cyano analogue.[14]

Studies of the solvolysis of the parent (**1a**) and 1-alkyl-substituted 2-adamantyl bromides (**1b–e**-Br) and sulfonates (**1b–e**-OSO_2Ar) have been interpreted to indicate that the ionization of **1b–e** is anchimerically assisted (K_Δ process[15]) and involves σ-bridged ions (**2b–e**) as intermediates.[16] It was stated that **1b** provides a "textbook" example of "nonclassical" ion, . . . "free from the many anomalies of the 2-norbornyl system".[16c] A subsequent investigation of related substrates carrying deactivating substituents (**1f,g**)[17] led the present writer to question[14] some of the conclusions expressed by previous workers.[16] Such a viewpoint elicited interest[18] as well as criticism.[19] Most of the latter concerned the existence[14] of a relationship between rearrangement and rate enhancement in the solvolysis of 1-substituted 2-adamantyl substrates (**1**). It was considered[14] that, if the formation of rearranged product is due to bridging, then the measured solvolysis rate is faster than the value expected in the absence of bridging. A precise mathematical relationship between rates and amount of rearrangement for **1** could not be deduced,[20] but in the same solvent and under the same conditions a larger amount of rearranged product possibly reflects a larger acceleration.[14] In other words, if two phenomena (rate enhancement and rearrangement) are produced by the same cause (bridging) they are necessarily related. As this point was also recognized by the previous workers,[21] it needs no further elaboration. One valid observation remained, however: In the solvolysis of the cyano derivative (**1g**-OTres), a rearranged product, 8-cyanotricyclo[4.3.1.$0^{3,8}$]decan-4-*exo*-ol (8-cyano-4-*exo*-protoadamantanol) (*exo*-**3**) was formed (38%) along with the starting alcohol (**1g**-OH).[14] The absence of the



1 (X = OH, Br, OTs, OTres)

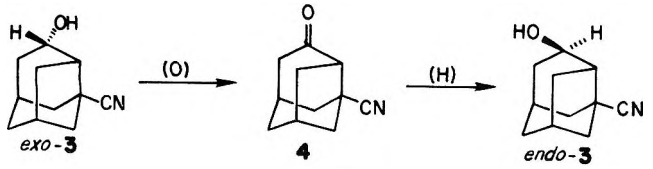


2

a R = R' = H
b R = Me, R' = H
c R = Et, R' = H
d R = *i*-Pr, R' = H
e R = *t*-Bu, R' = H
f R = H, R' = COO Me
g R = H, R' = CN

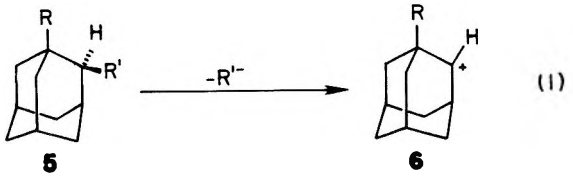
stereoisomeric *endo*-**3** was inferred from the fact that only one peak was observed on GLC on two different columns,[14] but a coincidence in retention time of two isomers could not be ruled out.

In order to remove any uncertainty the preparation of *endo*-**3** was undertaken. The rearranged product from solvolysis (*exo*-**3**)[14] was oxidized with the Jones reagent under mild conditions to give 8-cyano-4-protoadamantanone (**4**) as the only product. Sodium borohydride reduction of **4** at 0 °C led to a mixture of *endo*-**3** and *exo*-**3** in about 5:4 ratio. The



epimers could be separated by GLC, the endo isomer eluting first on a silicone-SE30 column. The same analysis conditions failed to reveal any *endo*-**3** in the solvolysis mixture from **1g**-OTres.[14] Thus, the rearranged product from **1g**-OTres is formed with the same stereospecificity as the rearranged product from 1b-OTs.[16c]

The similar behavior of **1b** and **1g** substrates could be rationalized either by admitting the intermediacy of σ-bridged ions in both, or by considering that ionization leads to a nonbridged ion in both cases and the rearrangement takes place after ionization.[14] It has been already shown that by accepting the first alternative we are led to the disturbing conclusion that the observed acceleration produced by a 1-methyl group in **1** is too small to reflect any significant stabilization by bridging in **12**.[14] In order to accept the second alternative we must identify the origin of the observed rate effect of the 1-methyl substituent. This rate acceleration (the point for 1b-OTres deviates upward by a factor of 13 from the least-squares $\rho^*\sigma^*$ line drawn through the points for **1a-**, **1f-**, and **1g**-OTres[14]) was previously explained by bridging.[16] However, it has been shown that neighboring alkyl substituents exert a magnified steric effect in the solvolysis of rigid, polycyclic substrates.[22] In order to probe the existence of a steric effect upon rates in **1b–e**, the variation of strain energy on ionization was calculated for the reaction shown in eq 1. This is, in fact,



(1)

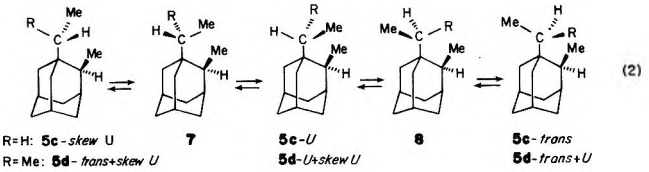
a R=H; **b** R=Me; **c** R=Et; **d** R=*i*-Pr; **e** R=*t*-Bu

the standard procedure used in previous studies of effects of steric strain upon solvolysis rates.[13]

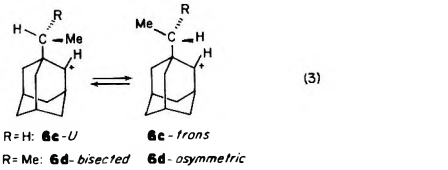
In formula **5** (eq 1) R′ represents the leaving group. Ideally, the force field should include the actual leaving group employed in solvolysis. Recently, attempts have been made to extend the force field calculations to heteroatom-substituted molecules.[23] However, the agreement with the experiment was consistently poorer than that secured for hydrocarbons.[23a,c,24] A more successful approach has been to use the force field for hydrocarbons, either "engrossing" a carbon atom to the size of the heteroatom,[25] or trying to match the heteroatom or group by an isosteric alkyl group.[26a] Most of the previous correlations of solvolysis rates[13] have used hydrogen for the leaving group. This admitted simplification[13c] masked the steric interactions involving the leaving group and was recently criticized.[27] In the case of 2-alkyl-2-adamantyl substrates[13c] the probable result was too high[27] a slope for the line correlating the solvolysis rates with the strain energy variations (Δ (strain)) (vide infra).

Looking for a measure of comparison between the size of a halide or sulfonate and that of an alkyl group, it became clear that conformational energies (*A* values) were not suitable for the following reasons: (1) The *A* values are determined in a flexible system (cyclohexane) which can flatten or pucker to minimize steric interactions; this is not the case with **5**. (2) The *A* values vary widely with the solvent, in most cases systematically with the solvent polarity.[28] (3) The equatorial/axial preference of a substituent is significantly influenced by its polarity; the more polar substituents, even when much bulkier, have a larger proportion of axial conformer.[29] (4) The *A* values are largely determined by 1,3-diaxial interactions in the axial conformer. This is constant throughout our reaction series (eq 1), while the 1,2-skew interaction between R and R′ increases. The two kinds of interaction do not have a parallel variation.[30]

A better measure of the space requirements of substituents are probably the van der Waals radii. Indeed, correlation of a large number of reaction series has been achieved using steric constants derived from van der Waals radii.[31] On that basis, CH_3 (about as large as Cl, but smaller than Br) is an acceptable model for the leaving group, although it is too small to represent a sulfonate ester group. Previously, CH_3 has been used to model Br and neopentyl to model OSO_2Ar in a correlation of tosylate/bromide solvolysis rate ratios with Δ(strain) on ionization.[26a] The correlation was only fair, but the goal was probably too ambitious, with the systems investigated varying widely.[26b] More recently, to detect steric acceleration in the solvolysis of cyclooctyl tosylate,[32] CH_3 was used to mimic the leaving group. The same approach was adopted in the present work (**5**, R′ = CH_3, eq 1). The latest force field developed at Princeton University[2a] was employed.[33] Results of the calculations are shown in Table I. Since there are three possible rotamers each for compounds **5c** and **5d** (eq 2) and two possible rotamers each for ions **6c** and **6d** (eq 3), the strain ener-



(2)



(3)

gies for all these were calculated.[34] The barriers for rotamer interconversions were tested for compound **5c** by calculating the strain energies and heats of formation for the eclipsed conformers **7** and **8** (eq 2 and Table I).

The variation of strain energy on ionization (eq 1) is calculated in Table 1 as Δ(strain) = $\Delta H°$(strain **5**) − $\Delta H°$(strain **6**). Since the barriers for rotamer interconversion are small in comparison with the activation energy of the solvolysis,[16a] the strain relief for the ionization of **5c** and **5d** was calculated from the strain energies of individual conformers by the approach used previously to evaluate activation energies for reactions in systems with mobile equilibrium in both reactants and products.[35] (Using in calculation the values for the lowest energy conformers,[13c] or the average strain energy for each state, did not alter the correlation significantly.)

Examination of Table I reveals that Δ(strain) increases markedly with the size of the alkyl group at C-1 (R). As intuitively expected, the greatest difference is between H and Me,[36] and between *i*-Pr and *t*-Bu.

For a quantitative correlation, the solvolysis rates measured

Table I. Strain Energies for Hydrocarbons and Carbocations (eq 1, R′ = CH_3) and Solvolysis Rates of 1-Alkyl-2-adamantyl Tosylates

structure	registry no.	$\Delta H_f°$, kcal/mol	$\Delta H°$(strain), kcal/mol	Δ(strain)[a]	log k[b]
5a		−37.94[c]	8.56[c]	−0.65	−7.620
6a	21410-12-8	−25.08	9.21		
5b		−46.05[c]	8.64[c]	0.65	−6.078
6b	67011-20-5	−34.49	7.99		
5c-skew U	29521-81-1	−49.28	10.54		
5c-U		−47.47	12.35		
5c-*trans*		−48.85	10.97	1.17[d]	−5.564
6c-*trans*	66966-43-6	−38.06	9.55		
6c-U		−38.03	9.58		
5d-*trans* + skew U	34529-25-4	−52.85	14.05		
5d-U + skew U		−51.40	15.50		
5d-*trans* + U		−51.04	15.86	2.55[d]	−5.089
6d-asymmetric	66966-44-7	−43.06	11.63		
6d-bisected		−42.36	12.33		
5e	66966-45-8	−54.75	20.34	5.13	−3.668
6e	66966-46-9	−47.67	15.21		
7 (R = H)[e]		−41.76	18.06		
8 (R = H)[f]		−45.79	14.95		

[a] Positive value means strain relief on ionization. [b] 80% ethanol, 25 °C.[16a] [c] From E. M. Engler, Ph.D. Thesis, Princeton University, 1973. [d] See text. [e] The actual barrier was found for a dihedral angle C2–C1–C11–C12 = −4.40° (i.e., toward **5c**-U). $\Delta H_f°$ = −41.68, $\Delta H°$(strain) = 18.14. [f] Dihedral angle C8–C1–C11–C12 = −1.30°. The actual barrier was not established, but it cannot be significantly different in energy.

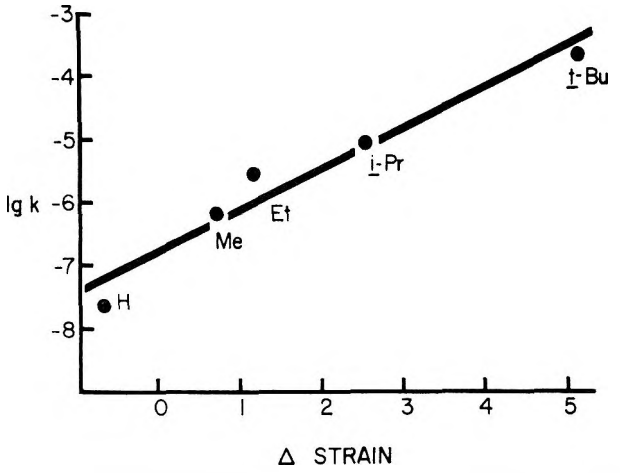


Figure 1. Plot of the log of rate constants for the solvolysis (80% ethanol, 25 °C) of 1-alkyl-2-adamantyl tosylates vs. the relief of strain energy calculated for eq 1. The straight line (least-squares fit) is represented by eq 4.

for compounds **1b–e** relative to the parent compound **1a** should be dissected in contributions of the polar and steric effects of β-alkyl substituents. It has been shown previously that the solvolysis of 2-adamantyl substrates (**1**) has an appreciable sensitivity to polar effects ($\rho^* = -4.09$).[14] However, as a first approximation it was decided to use the *measured* (nondissected) rates. This leads to a calculated sensitivity of rates to steric effects (for a linear relationship[37] that is the slope of the log $k = f(\Delta(\text{strain}))$ plot), which is too high.[27] The data are correlated by eq 4 (represented in Figure 1).

$$\log k = 0.63\Delta(\text{strain}) - 6.73$$
$$r = 0.9693;\ \text{SD} = 0.271 \qquad (4)$$

Although polar effects were not substracted, the slope of this line is rather low: 0.63 vs. 1.23 for the solvolysis of 2-alkyl-2-adamantyl *p*-nitrobenzoates.[13c] While the difference might indicate a higher sensitivity to steric effects for the latter reaction series, it is more probable that neglecting the steric effects of the leaving group in that study[13c] was responsible for at least a part of the difference.[27] The slope found for the present reaction series is also smaller than the one found for the acid-catalyzed dehydration of 2-alkyl-2-adamantanols.[27] Possibly, the leaving group steric effect was not fully accounted for by the model chosen in that study either.

The comparatively large effect of a β-alkyl group (particularly of a β-methyl group) upon solvolysis rates constituted the central evidence around which the case for a bridged intermediate in the solvolysis of **1b–e** has been built.[16a–c] As it was already pointed out,[14] the stereospecificity of the rearranged product formation does not require σ bridging; in fact, stereospecificity was found in polycyclic systems for reactions in which bridging can play no role.[7b,10,38] It is also noteworthy that the total stereoselectivity in the formation of rearranged product in the solvolysis of **1b** is accompanied by an *incomplete* stereoselectivity in the formation of nonrearranged product (**1b**-OH). The predominant retention in the latter case[39] is consistent with the absence of a bridged intermediate since, as noted by Schleyer,[40] retention is expected in limiting solvolysis of polycyclic systems like 2-adamantyl,[41] or even of acyclic tertiary systems.[40]

The central point of the debate[14,16] about the solvolysis of adamantyl (**1a**) and 1-alkyl-2-adamantyl substrates (**1b–e**) has been the contention[16] that introduction of a 1-alkyl group changes the nature of the process from essentially limiting (k_c process[15]) for **1a** [16b,c,40,41b] to anchimerically assisted, involving a bridged ion intermediate (**2b**), for **1b**.[16,42] This was easily rationalized, since a bridged intermediate from **1a** would be a hybrid between two structures differing by about 11 kcal/mol in energy,[16b] while for **2b** the two limiting structures should be nearly equal in energy.[16c] Yet, introduction of a 1-methyl group only insignificantly changes the stereoselectivity for the unrearranged product, from 64–84% retention[16b,41a] to 90% retention.[39] On the other hand, the rearranged product is, in the limits of sensitivity of the GLC analysis, exclusively exo from both **1a** and **1b**. Clearly, the stereospecificity in the formation of protoadamantyl product cannot be invoked as an argument for the intervention of **2b**. The present results indicate that the acceleration produced by β-alkyl groups in the solvolysis of secondary 2-adamantyl substrates has a steric origin, just as the acceleration produced

by the alkyl groups in the solvolysis of tertiary[43] 2-adamantyl substrates does.[13c,27] Therefore, the conclusion[14] that bridging in the solvolysis of **1b–e** is at best marginal,[44] or more probably absent altogether, unquestionably holds.

Experimental Section

General. The NMR spectra were recorded at 60 MHz (Varian A-60A instrument). High resolution mass spectra were determined at 70 eV (AEI-MS9 instrument), GLC–mass spectra were also done at 70 eV on an E. I. duPont 21-491 instrument. Melting points are uncorrected.

8-Cyano-4-protoadamantanone (4). Jones reagent was prepared from 4.575 g of CrO_3, 7.247 g of 94% H_2SO_4, and 15.20 g of water. 8-Cyano-4-exo-protoadamantanol (exo-3)[14] (0.0492 g) dissolved in acetone (1 mL) was cooled in an ice water bath and Jones reagent was added dropwise, with magnetic stirring. Each drop was added after the previous one had reacted completely (1–3 min). When the yellow color persisted for more than 10 min (ca. 7 drops were used) methanol was added (3 drops) and the mixture was stirred for 5 min. The solvent was evaporated at room temperature under a stream of nitrogen, then the solid residue was extracted several times with CH_2Cl_2. Drying and evaporation of solvent gave a white solid, homogeneous on TLC (4 can be separated from *exo*-**3**, *endo*-**3**, and 1-cyano-2-adamantanol on E. Merck silica gel plates, using 4:1 benzene–ethyl acetate as eluent). Yield 0.046 g (93%); mp 206–208.5 °C (from heptane); IR (KBr disk) 2940 (s), 2900, 2870, 2850, 2228, 1713 (vs), 1460, 1400, 1348, 1335, 1285, 1230, 1215, 1165, 1090, 1028, 970, 850, 832 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.30, with peaks at 1.95 and 2.08 (8 H); 2.30–2.83, with a peak at 2.47 (4 H), and 2.88–3.21 (1 H). Anal. Calcd for $C_{11}H_{13}NO$: M, 175.0997. Found: M 175.0991 (by high resolution MS).

8-Cyano-4-*endo*- (*endo*-3) and 8-Cyano-4-*exo*-protoadamantanol (*exo*-3). Sodium borohydride (0.010 g) was added to a solution of **4** (0.043 g) in anhydrous methanol (1.5 mL), at 0 °C. The mixture was stirred at 0 °C for 3 h, then for 3 h at room temperature. Acetic acid (2 drops) was added, the solvent was evaporated to dryness at room temperature under a stream of nitrogen, then water (1 drop) was added and the mixture was extracted several times with ether. The GLC of the dried (Na_2SO_4) solution (3% silicone SE-30, 1.8 m × 3 mm o.d., 120°) indicated a mixture of *endo*-**3** and *exo*-**3** (eluted in that order) in ca 5:4 ratio. Evaporation of the solvent left a solid (0.038 g, 87% yield): IR (KBr disk) 3455, 2910, 2860, 2220, 1455, 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.15–3.00 (complex, 14 H), 3.93–4.36 (m, 1 H); mass spectra[45] (determined by GLC–MS) for *endo*-**3** 177 ($M^{+}\cdot$) (4), 159 (100), 149 (17), 144 (16), 134 (16), 130 (15), 118 (26), 117 (73), 107 (20), 106 (22), 105 (23), 104 (34), 93 (33), 92 (44), 91 (33), 80 (32), 79 (24), 77 (17), 67 (19), 57 (15), 56 (19), 55 (17), 41 (19), 39 (15); MS for *exo*-**3**[46] 177 ($M^{+}\cdot$) (1), 159 (91), 144 (19), 118 (35), 117 (100), 106 (15), 105 (28), 104 (43), 93 (27), 92 (40), 91 (26), 81 (18), 80 (34), 79 (20), 67 (16), 57 (19), 56 (20), 41 (25), 39 (17).

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Registry No.—*exo*-**3**, 66966-47-0; *endo*-**3**, 67010-36-0; **4**, 66966-48-1.

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(42) Thus, it was stated that "unlike the secondary protoadamantyl and 2-adamantyl series, the bridged ion (i.e., **2b**) dominates the chemistry of" **1b** and the tertiary protoadamantyl substrates.[16c]
(43) For the reaction of tertiary substrates,[13c,27] the steric effect observed was also that of β and γ substituents, since the variable substituent was CRR'R'', with R = R' = R'' = H for the "parent" compound.
(44) Following our previous article (ref. 14) and the solvolysis study on optically active **1b**, the original workers in the field describe presently this system as involving a weakly bridged ion **2b** (ref 19), in contrast to a model nonclassical ion "which behaves according to textbook expectations", as was stated originally (ref 16c).
(45) With the exception of the parent peak, only the peaks with an intensity (in parentheses) higher than 15% of the intensity of the base peak are listed.
(46) The conditions used for the present GLC–MS experiments (5% silicone SP2250, 3 m × 3 mm o.d., at 170 °C with 30 mL/min He as carrier gas) ensured a more uniform elution of each component from the column (broader, yet well-resolved peaks) than in the previous work.[14] Whenever the relative intensities of fragment ions differ from those reported,[14] it is believed that the present values are more reliable.

Tautomerism and Dissociation of 4-Arylazo-1-naphthols in Various Solvents[1]

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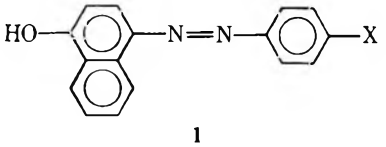
The tautomerism of 4-(4′-substituted-phenylazo)-1-naphthol [azo form (1) vs. hydrazone form (2)] is estimated by means of electronic spectra in various solvents. With electron-donating substituents the azo form is stabilized, while electron-withdrawing ones stabilize 2. The azo form is stabilized in pyridine, acetone, ethanol, and methanol, while the hydrazone form predominates in chloroform and acetic acid based on the equilibrium in benzene as standard. The equilibrium fits the Yukawa–Tsuno equation, $\log K/K_0 = \rho(\sigma^0 + r\Delta\bar{\sigma}_R^+)$, r and ρ values being determined in the solvent system mentioned above. The proton-donating solvent (chloroform) gives a larger r value; the values for the proton-acceptor solvents are smaller than that of benzene, the standard solvent. In polar aprotic solvents such as dimethyl sulfoxide and *N,N*-dimethylformamide 4-(4′-substituted-phenylazo)-1-naphthol is found to be present as a dissociated form.

Introduction

The physical properties of azo dyestuff (e.g., tone, color) are closely related with the tautomerism of the dyes. 4-(4′-Substituted-phenylazo)-1-naphthols (4-azo dyes) prepared by the coupling reaction of 4-substituted benzenediazonium salts with 1-naphthol are profoundly interesting as fundamental azo compounds. They may have two tautomeric isomers, 1 and 2, as shown in eq 1. The tautomeric equilibration



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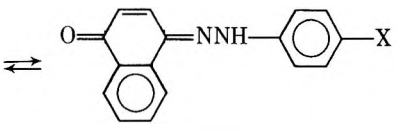


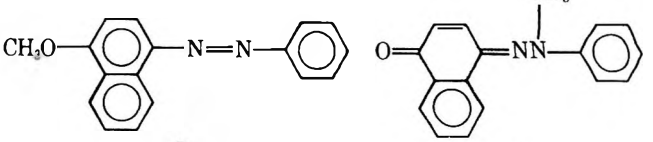
2 (1)

X = OCH_3, CH_3, H, Cl, NO_2

is found to depend upon their substituents as well as on solvents.[3–5] Every study reported so far has been qualitatively treated. In this paper we wish to describe experimental results on the tautomerism investigated quantitatively by means of electronic spectra and to discuss the effects of substituents and solvents.

Experimental Section

Materials. The 4-azo dyes[6,7] 1-methoxy-4-phenylazonaphthalene (3)[8] and 1,4-naphthoquinone-*N*-methylphenylhydrazone (4)[9] were prepared according to the literature.



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4

Methods. Spectra were taken on a Shimadzu MPS-50L spectrometer in 2×10^{-5} M solution with 10-mm cuvettes; Beer's law was shown to be valid at this concentration.

The 1/2 ratios were estimated by assuming that 3 and 4 represent the extreme forms for 1 and 2 and that the spectral shape of 1 and 2 and the ratios of the molecular extinction coefficients of 1 and 2 at the maximum absorptions are constant irrespective of the kinds of substituents when recorded in the same solvent.

Results and Discussion

Figure 1a exhibits the electronic spectra of 4-(4′-methox-

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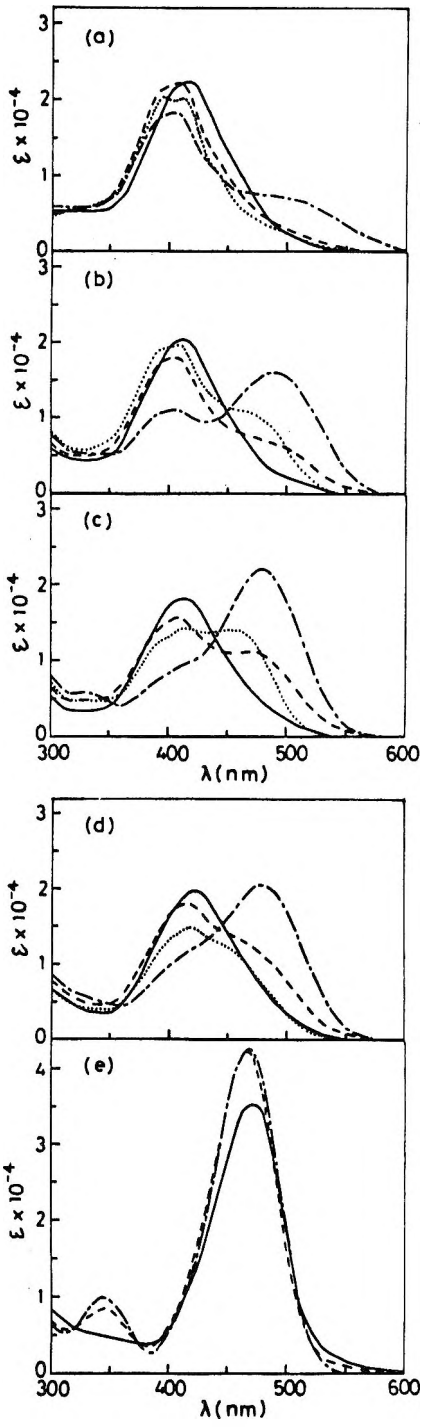


Figure 1. Electronic spectra of 4-(4′-substituted-phenylazo)-1-naphthols: (a) 4′-OCH_3 derivative; (b) 4′-CH_3 derivative; (c) H derivative; (d) 4′-Cl derivative; (e) 4′-NO_2 derivative. Solvents: — C_5H_5N; - - - CH_3OH; · · · C_6H_6; - · - · CH_3COOH.

yphenylazo)-1-naphthol (4′-OCH_3 derivative) in typical solvents. In pyridine, methyl alcohol, or benzene the sole band appeared at about 410 nm ascribable to the azo form (1);[10] the absorption (~480 nm) due to the hydrazone form (2) was virtually negligible. In acetic acid form 1 was still favored, though the latter peak was observed slightly. The electronic spectra of 4-(4′-methylphenylazo)-1-naphthol (4′-CH_3 derivative) is shown in Figure 1b. Small absorptions at ~480 nm were recognized in methyl alcohol and benzene, whereas in acetic acid this was preferred. The unsubstituted compound, 4-phenylazo-1-naphthol (H derivative), gave the spectra shown in Figure 1c. The band at 480 nm was observed even in methyl alcohol. In benzene the absorbance at 410 nm was approximately equal to that at 480 nm. In acetic acid the longer wavelength absorption predominated. The 4′-chloro derivative gave the spectra exhibited in Figure 1d. The 480-nm absorption appeared as a discernible shoulder even in pyridine. The nitro derivative showed the absorption near 480 nm only in every solvent used (Figure 1e).

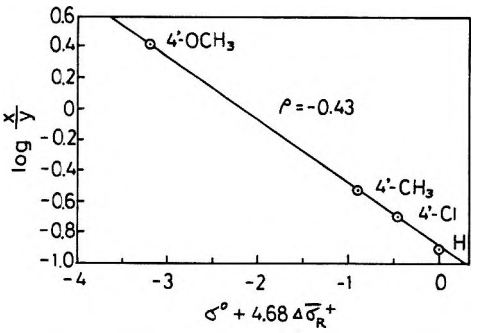


Figure 4. Relation of log K to $(\sigma^0 + r\Delta\bar{\sigma}_R^+)$ in CH_3COOH.

The spectrum of **3** (see Figure 2 of supplementary material) in various solvents exhibits the absorption maximum at 393–405 nm corresponding to the azo form (1); on the other hand the absorption maximum of **4** (460–469 nm, see Figure 3 of supplementary material) may be related to the hydrazone form (2).

Tables I and II exhibit the molecular extinction coefficients (ϵ_{410} and ϵ_{480}) and wavelengths (λ_{410} and λ_{480}) at the absorption maxima of 4-azo dyes, and the ratios of the molecular extinction coefficients ($\epsilon_{410}/\epsilon_{480}$), respectively. From the $\epsilon_{410}/\epsilon_{480}$ values, the 1/2 ratios were determined in the following way.

If the molecular extinction coefficients of 1 (or 2) at about 410 and 480 nm in each solvent are expressed by ϵ_{410}^{azo} and ϵ_{480}^{azo} (or ϵ_{410}^{hyd} and ϵ_{480}^{hyd}), and the mole fractions of 1 and 2 by x and y, respectively, then eq 2 should be:

$$\frac{\epsilon_{410}}{\epsilon_{480}} = \frac{x\epsilon_{410}^{azo} + y\epsilon_{410}^{hyd}}{x\epsilon_{480}^{azo} + y\epsilon_{480}^{hyd}} = \frac{\frac{x}{y}\epsilon_{410}^{azo} + \epsilon_{410}^{hyd}}{\frac{x}{y}\epsilon_{480}^{azo} + \epsilon_{480}^{hyd}} \quad (2)$$

Substituting a, b, and c for $\epsilon_{410}^{azo}/\epsilon_{480}^{azo}$, $\epsilon_{410}^{hyd}/\epsilon_{480}^{hyd}$, and $\epsilon_{410}^{azo}/\epsilon_{480}^{hyd}$, respectively, eq 2 yields the equation

$$\frac{\epsilon_{410}}{\epsilon_{480}} = \frac{\frac{x}{y}\epsilon_{410}^{azo} + b\epsilon_{480}^{hyd}}{\frac{1}{a}\frac{x}{y}\epsilon_{410}^{azo} + \epsilon_{480}^{hyd}} = \frac{c\frac{x}{y} + b}{\frac{c}{a}\frac{x}{y} + 1} = a - \frac{a-b}{\frac{c}{a}\frac{x}{y} + 1} \quad (3)$$

Figure 1 shows that the 4′-OCH_3 derivative exists almost 100% as 1 in pyridine, acetone, ethanol, methanol, or benzene. Similarly, the 4′-CH_3 derivative takes only the azo form (1) in pyridine. In this case the $\epsilon_{410}/\epsilon_{480}$ ratio (Table II) is equal to a ($= \epsilon_{410}^{azo}/\epsilon_{480}^{azo}$). On the other hand, the hydrazone form (2) is completely formed for the 4′-nitro derivative (Figure 1e). Therefore, $\epsilon_{410}/\epsilon_{480}$ (Table II) is equal to b ($= \epsilon_{410}^{hyd}/\epsilon_{480}^{hyd}$) in every solvent. The value for chloroform and acetic acid was estimated to be 5.2, the average value for other solvents.[11]

The ratio of the molecular extinction coefficients of **3** to **4** (Table III), $\epsilon_{410}^{azo}/\epsilon_{480}^{hyd} = c$, is listed in Table IV as well.

On the assumption that a, b, and c values are independent of the kind of substituents in the same solvent the 1/2 ratio can be calculated according to eq 3 (Table V). The assumption is valid in the case of 4′-OCH_3 and 4′-CH_3 derivatives in pyridine (Table II).

The logarithm of the equilibrium constant K ($= x/y$) was plotted against the substituent constant to give a linear relationship satisfying the Yukawa–Tsuno equation:[12]

Table I. Molecular Extinction Coefficients (ϵ_{410} and ϵ_{480}) and Wavelengths (λ_{410} and λ_{480}) at the Absorption Maxima of Azo and Hydrazone forms of 4-(4′-Substituted-phenylazo)-1-naphthols in Various Solvents

	substituent									
	4′-OCH_3		4′-CH_3		H		4′-Cl		4′-NO_2	
solvent	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm
pyridine	22.5	418	20.6	413	18.2	414	19.8	423	8.2	410[b]
	4.7	480[a]	4.3	480	6.1	470	9.4	470	34.6	475
acetone	23.0	412	22.0	408	19.0	408	19.1	418	10.5	405[c]
	3.5	480[a]	5.5	480	9.1	470	10.0	470	49.0	462
ethyl alcohol	22.6	413	18.0	410	17.4	410	18.0	420		410[b]
	4.8	480[a]	5.9	480	9.8	470	9.4	470		467
methyl alcohol	22.2	410	17.9	406	15.6	408	18.0	415	9.4	410[b]
	4.6	480[a]	7.3	480	11.2	470	12.4	470	42.2	470
benzene	20.3	412	19.8	408	14.2	412	15.0	412		400[c]
	3.8	480[a]	10.6	470	12.9	470	9.7	470		457
chloroform	18.5	410	11.9	412	11.0	410	13.3	410		405[c]
	6.8	475	13.4	475	20.0	467	17.0	463		463
acetic acid	18.2	408	11.0	410	9.2	410	10.9	410	9.5	410[b]
	7.2	490	16.2	490	22.0	480	20.5	480	42.4	470

[a] The average value (480 nm) of λ_{max} in chloroform and pyridine. [b] The average value (410 nm) for other derivatives in various solvents is listed. [c] The estimated value is shifted according to the absorption of the hydrazone form.

Table II. Ratios of Molecular Extinction Coefficients ($\epsilon_{410}/\epsilon_{480}$) at the Absorption Maxima of Azo and Hydrazone Forms of 4-(4′-Substituted-phenylazo)-1-naphthols in Various Solvents

	substituent				
solvent	4′-OCH_3	4′-CH_3	H	4′-Cl	4′-NO_2
pyridine	4.79	4.79	2.98	2.11	0.237
acetone	6.57	4.00	2.09	1.91	0.214
ethyl alcohol	4.71	3.05	1.78	1.91	0.240[a]
methyl alcohol	4.83	2.45	1.39	1.45	0.223
benzene	5.34	1.87	1.10	1.55	0.250[a]
chloroform	2.72	0.888	0.550	0.782	0.236[a]
acetic acid	2.53	0.679	0.418	0.532	0.224

[a] Values were obtained at arbitrary concentrations because of slight solubility.

Table III. Molecular Extinction Coefficient (ϵ) and Wavelength (λ_{max}) at the Absorption Maximum of 1-Methoxy-4-phenylazonaphthalene and 1,4-Naphthoquinone-*N*-methylphenylhydrazone in Various Solvents

	1-methoxy-4-phenylazo-naphthalene		1,4-naphtho-quinone-*N*-methylphenyl-hydrazone	
solvent	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max} nm
pyridine	11.5	405	9.2	460
acetone	10.3	395	8.8	452
ethyl alcohol	11.0	395	9.8	462
methyl alcohol	11.6	393	10.6	460
benzene	9.8	400	7.1	460
chloroform	10.9	398	8.5	461
acetic acid	19.0	395	10.8	469

$$\log K/K_0 = \rho(\sigma^0 + r\Delta\bar{\sigma}_R^+) \quad (4)$$

where K_0 is the equilibrium constant of the H derivative and ρ and r are arbitrary constants. The $\Delta\bar{\sigma}_R^+$ value in eq 4 is defined as $\sigma^+ - \sigma^0$ where the σ^+ value is that given by Brown and Okamoto[13] and σ^0 by Taft et al.[14] For example, Figure 4 exhibits the relation in acetic acid, in which r and ρ were calculated to be 4.68 and −0.43, respectively. Similar relations were obtained for other solvents; r and ρ values for each solvent are listed in Table VI. The log $(-\rho)$ was plotted against the log r to give a very good linear inverse correlation.

Table IV. The Values a, b, and c in Various Solvents

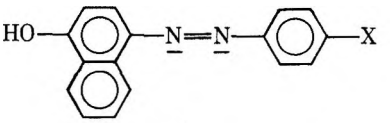
solvent	*a*	*b*	*c*
pyridine	4.79	0.237	1.25
acetone	6.57	0.214	1.17
ethyl alcohol	4.71	0.240	1.12
methyl alcohol	4.83	0.223	1.09
benzene	5.34	0.250	1.38
chloroform	52.[a]	0.236	1.28
acetic acid	5.2[a]	0.224	1.76

[a] The average of the first five values in the column.

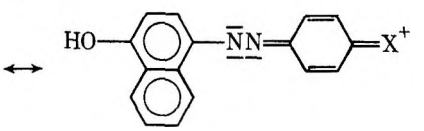
As shown in Table V, the percentage of 1 increased in the following order (eq 5) in each solvent system.

$$4'\text{-}NO_2 < H \approx 4'\text{-}Cl < 4'\text{-}CH_3 < 4'\text{-}OCH_3 \quad (5)$$

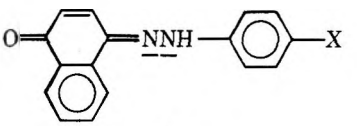
This trend can be explained in terms of the following discussion. The azo group (–N=N–) in **1** is an electron acceptor and the imino group (–NH–) in **2** is an electron donor, so that **1** is stabilized by the more electron-donating 4′-substituent, while an electron-accepting group stabilizes **2**. Furthermore, the good linear relation of the equilibrium constant K to sub-



1



(6)



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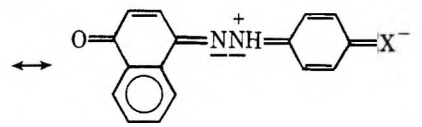


(7)

Table V. Ratio (1/2) and Percentage of 1 of 4-(4′-Substituted phenylazo)-1-naphthols in Various Solvents

	substituent									
	4′-OCH_3		4′-CH_3		H		4′-Cl		4′-NO_2	
solvent	1/2	% of 1	1/2	% of 1	1/2	% of 1	1/2	% of 1	1/2	% of 1
pyridine	∞	100	∞	100	5.80	85	2.67	73	0	0
acetone	∞	100	8.28	89	2.36	70	2.05	67	0	0
ethyl alcohol	∞	100	7.11	88	2.21	69	2.51	71	0	0
methyl alcohol	∞	100	4.15	81	1.50	60	1.61	62	0	0
benzene	∞	100	1.81	64	0.777	44	1.33	57	0	0
chloroform	4.07	80	0.611	38	0.271	21	0.499	33	0	0
acetic acid	2.56	72	0.300	23	0.123	11	0.198	17	0	0

Table VI. The Values r and ρ in Various Solvents

solvent	r	ρ
acetone	1.45	−1.41
ethyl alcohol	2.07	−1.06
methyl alcohol	1.94	−0.96
benzene	6.85	−0.29
chloroform	17.23	−0.11
acetic acid	4.68	−0.43

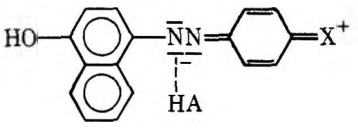
stituent constant as well as the relatively high r value suggest a relatively large contribution of the resonance form. That is to say, with an electron-donating group (X) the stability of **1** is increased by the resonance shown in eq 6. On the other hand, the resonance shown in eq 7 raises the stability of **2** on the electron acceptor, such as a nitro group.

The percentage of **1** increased in the following order of solvents.

acetic acid < chloroform < benzene < methyl alcohol < ethyl alcohol ≈ acetone < pyridine (8)

We considered this effect as follows. The tautomeric equilibria are influenced considerably by the ability of external hydrogen bonds between each tautomer and suitable solvents; the tautomers are stabilized to differing degrees by such bonds. The hydroxy group (–OH) in **1** is capable of stronger hydrogen bonding than the imino group (–NH–) in **2** in the proton-acceptor solvents such as pyridine, acetone, and alcohols as compared with benzene.[15] The imino group (–NH–) in **2** is so basic that **2** is more stabilized in the proton-donor solvents such as acetic acid and chloroform than in the proton-acceptor solvents.

The value r varied over a wide range depending on the solvent. The proton-donor solvent (HA), chloroform, showed a larger r value than benzene. The effect can be ascribed to the stabilization of **1** by the solvation indicated in **5**. On the other



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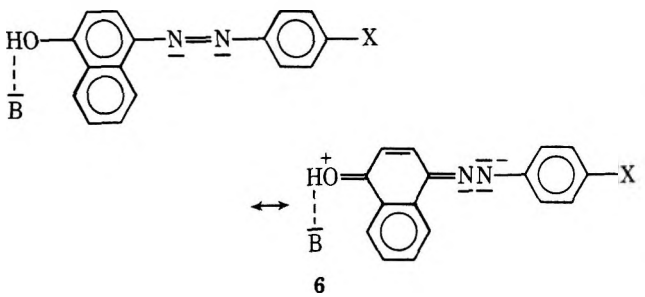
hand, in the proton-accepting solvent (B) the resonance (**6**) stands against that of eq 6, therefore the r value has become smaller than on benzene.



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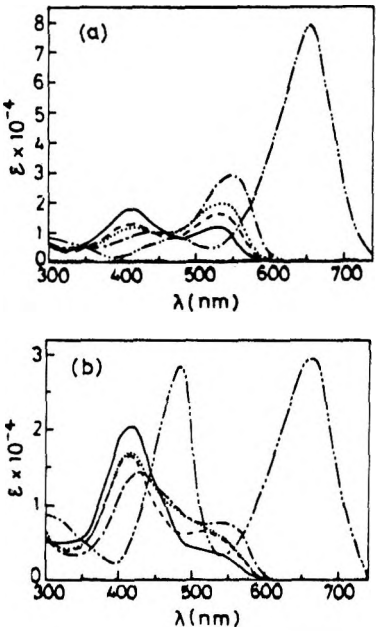
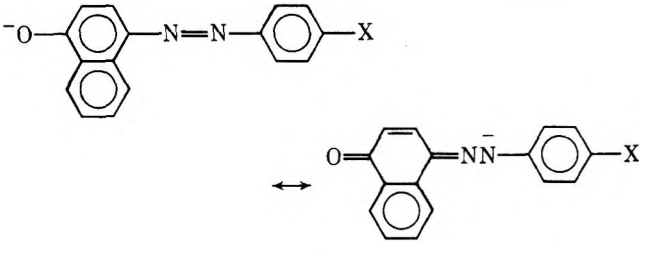


Figure 5. Electronic spectra of 4-(4′-substituted-phenylazo)-1-naphthols in (a) DMF and (b) Me_2SO: — 4′-OCH_3 derivative; - - - 4′-CH_3 derivative; ··· H derivative; – · – · 4′-Cl derivative; – · · – · · 4′-NO_2 derivative.

The electronic spectra of 4-azo dyes in DMF and Me_2SO (Figure 5), respectively, possess the absorption band at comparably longer wavelength than those in the above mentioned seven solvents. In particular the band appeared remarkably well in DMF: 4′-OMe, 530 nm; 4′-Me, 532 nm; H, 535 nm; 4′-Ch, 550 nm; 4′-nitro, 654 nm. These bands may be ascribed to the anionic form **7**. Therefore we measured the spectra of



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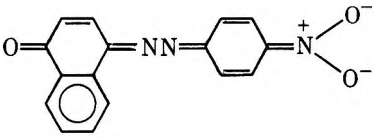
H and 4′-nitro derivatives (Figures 6 and 7, respectively, supplementary material) in 50 vol % pyridine–water and 0.1 N NaOH (50 vol % pyridine–water) solutions in which the phenolate ion was expected to be produced (pK_a[16] of H derivative is 9.7, 4′-nitro derivative 10.1). The absorption due to tautomers **1** and **2** disappeared completely and a new peak at longer wavelength (H derivative 510 nm; 4′-nitro derivative 625 nm) appeared. Similarly the band of longer wavelength in DMF and Me_2SO can be correlated with the band in 0.1 N NaOH (50 vol % DMF–water) and 0.1 N NaOH–DMF solutions (H derivative, see Figure 8 of supplementary material;

4′-nitro derivative, see Figure 9 of supplementary material), and 0.1 N NaOH (50 vol % Me_2SO–water) and 0.1 N NaOH–Me_2SO solutions (H derivative, see Figure 10 of supplementary material; 4′-nitro derivative, see Figure 11 of supplementary material). The remarkable red shift of the band of the 4′-nitro derivative can be ascribed to the lengthening of the conjugated system in the form **8**. Thus, the 4-azo dyes



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dissolved in DMF and Me_2SO are converted to the phenolate ion (**7**) probably due to the high dielectric constant and high basicity of the solvent. The discussion may be supported from the absorption maximum of the electronic spectra (see Figure 12 of supplementary material) of **3** and **4** in DMF and Me_2SO, which are quite different from the spectra in Figure 5. The longer wavelength absorption is not due to **1** or **2**.

Registry No.—**1** (X = OCH_3), 3009-53-8; **1** (X = CH_3), 5098-99-7; **1** (X = H), 3651-02-3; **1** (X = Cl), 7252-64-4; **1** (X = NO_2), 5290-62-0; **2** (X = OCH_3), 32159-06-1; **2** (X = CH_3), 36853-51-7; **2** (X = H), 19059-71-3; **2** (X = Cl), 36853-56-2; **2** (X = NO_2), 36853-60-8; **3**, 24390-69-0; **4**, 66881-37-6.

Supplementary Material Available: Figures 2, 3, and 6–12 of electronic spectra of compounds mentioned in the text (9 pages). Ordering information is given on any current masthead page.

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Photolysis and Thermolysis of Di-*n*-butylmalonyl Peroxide. Evidence for α-Lactone Intermediates[1]

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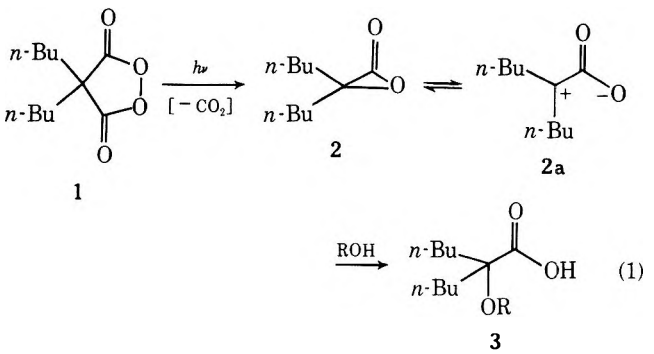
Photolysis and thermolysis of di-*n*-butylmalonyl peroxide (**1**) afford α-lactone **2** as a reaction intermediate. In a nonprotic solvent such as benzene or *n*-hexane, the α-lactone **2** polymerizes to polyester **5**, while in methanol or ethanol it is trapped nucleophilically in the form of α-alkoxy acid **3**. Some of the α-lactone decarbonylates into 5-nonanone (**4**), but only small amounts decarboxylate to give 4-nonene (**12**), presumably via its carbene. In the thermal decomposition of the malonyl peroxide **1** in methanol and ethanol, α-lactone formation is competed for by solvolytic reaction, leading to a complex product mixture of malonic half-ester **6** and its decarboxylated ester **7**, α,β-unsaturated ester **8**, α-hydroxy ester **9**, malonic acid **10**, and its decarboxylated acid **11**. This solvolytic process predominates over α-lactone formation in the thermolysis of the malonyl peroxide **1** in ethanol.

Several years ago we communicated[3] that photodecarboxylation of di-*n*-butylmalonyl peroxide (**1**) leads to α-lactones **2** as intermediates which can be trapped through their dipolar form **2a** with protic nucleophiles (eq 1). Subsequently, we showed[4] that in a matrix isolated form these elusive reaction



1 **2** **2a** **3** (1)

intermediates can be preserved to enable infrared characterization. By means of bis(trifluoromethyl) substitution at the α carbon, it was possible to isolate a stable α-lactone by discouraging formation of the dipolar form **2a** through electronic destabilization.[5] Other papers on the chemistry of malonyl peroxides include their vapor phase thermolysis[6] and their solvolysis with primary and secondary alcohols.[7] In this paper, we give a full account of the photo- and thermodecarboxylation of di-*n*-butylmalonyl peroxide.

Results and Discussion

When a 0.15 M solution of the malonyl peroxide **1** in benzene or *n*-hexane is irradiated at 350 nm in a Pyrex vessel, within 15–20 h its characteristic sharp carbonyl band at 1783 cm^{-1} is replaced by a broad carbonyl band at 1740 cm^{-1}. Removal of the solvent by distillation at reduced pressure afforded a solid residue, mp 138.5–140.5 (benzene) and 146–146.5 °C (*n*-hexane), identified as poly-3,3-di-*n*-butyloxi-

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Table I. Product Composition of the Photolysis of Malonyl Peroxide 1

solvent	concn (M)	$h\nu$ (nm)	time[c] (h)	volatile products (mol %)[a,b] 6	7	8[d]	9	10	11	3	4	12	residue[e] 5
MeOH	0.280	350	27	2.7	0.3	4.1	0.6	<0.1	0.2	86.2	4.4	1.0	9.0
MeOH	0.285	310	10	2.4	0.5	4.3	0.6	<0.1	0.6	87.9	1.2	1.9	11.0
EtOH	0.116	350	24	<0.1	<0.1	6.1	0.3	0.9	0.6	88.0	4.0	0.6	
EtOH	0.282	310	12	<0.1	0.3	6.0	0.9	1.2	1.1	85.1	3.2	1.6	23.0
C_6H_6[f]	0.150	350	15								5 9	3.5	89.0
n-C_6H_{14}[f]	0.150	350	15								8.8	7.3	82.0

[a] Relative composition of distilled, volatile products after treatment with diazoalkane. The RCH_2 group stands for the alkyl group of the solvent. [b] Quantitative VPC analysis was carried out under conditions CX-2 and AZ-1. [c] Time required for peroxide carbonyl band (1783 cm^{-1}) to disappear in the IR. [d] Cis,trans mixture. [e] Polyester, determined gravimetrically (wt %). [f] Absolute product composition.

Table II. Product Composition of the Thermolysis of Malonyl Peroxide 1

solvent	concn (M)	temp (°C)	time (h)	volatile products (mol %)[a,b] 6	7	8[d]	9	10	11	3	4	12	residue[e] 5
MeOH	0.300	140	2[c]	8.3	3.6	11.0	1.5	<0.1	27.0	47.8	0.5	0.3	22:0
MeOH	0.300	140	15	2.1	17.6	9.0	0.7	<0.1	27.0	47.2	1.1	<0.1	
EtOH	0.293	140	2[c]	0.4	1.3	5.1	0.9	<0.1	71.5	18.6	2.2		12.0
EtOH	0.293	140	25	<0.1	6.6	5.4	0.7	<0.1	68.3	18.2	0.8		
EtOH	0.293	140	45	<0.1	9.7	6.4	0.6	<0.1	65.4	17.0	0.9		
EtOH	0.293	130	2[c]	0.3	1.1	4.5	0.4	4.0	70.1	18.5	1.1		
EtOH	0.293	130	25	<0.1	3.7	4.4	0.5	<0.1	72.8	17.3	1.3		
C_6H_6	0.100	140	5[c]			60.0[f]					40.0		85.0
n-C_6H_{14}	0.150	140	6[c]			35.0[f]			16.1		26.4	<0.1	91.0

[a] Relative composition of distilled, volatile products after treatment with diazoalkane. The RCH_2 group stands for the alkyl group of the solvent. [b] Quantitative VPC analysis was carried out under conditions CX-2 and AZ-1. [c] Time required for peroxide titer to drop below 0.5% (iodometry). [d] Cis,trans mixture. [e] Polyester, determined gravimetrically (wt %). [f] $RCH_2 = CH_3$ due to esterification with diazomethane.

ran-2-one (**5**), i.e., the polyester derived from the α-lactone **2**. Its structure assignment rests on the correct elemental analysis and a molecular weight of 4996 (osmometry in $CHCl_3$), corresponding to ca. 29 α-lactone units. Lithium aluminum hydride reduction of the polyester **5** gave the expected 2-*n*-butylhexane-1,2-diol[8] in 72% yield.

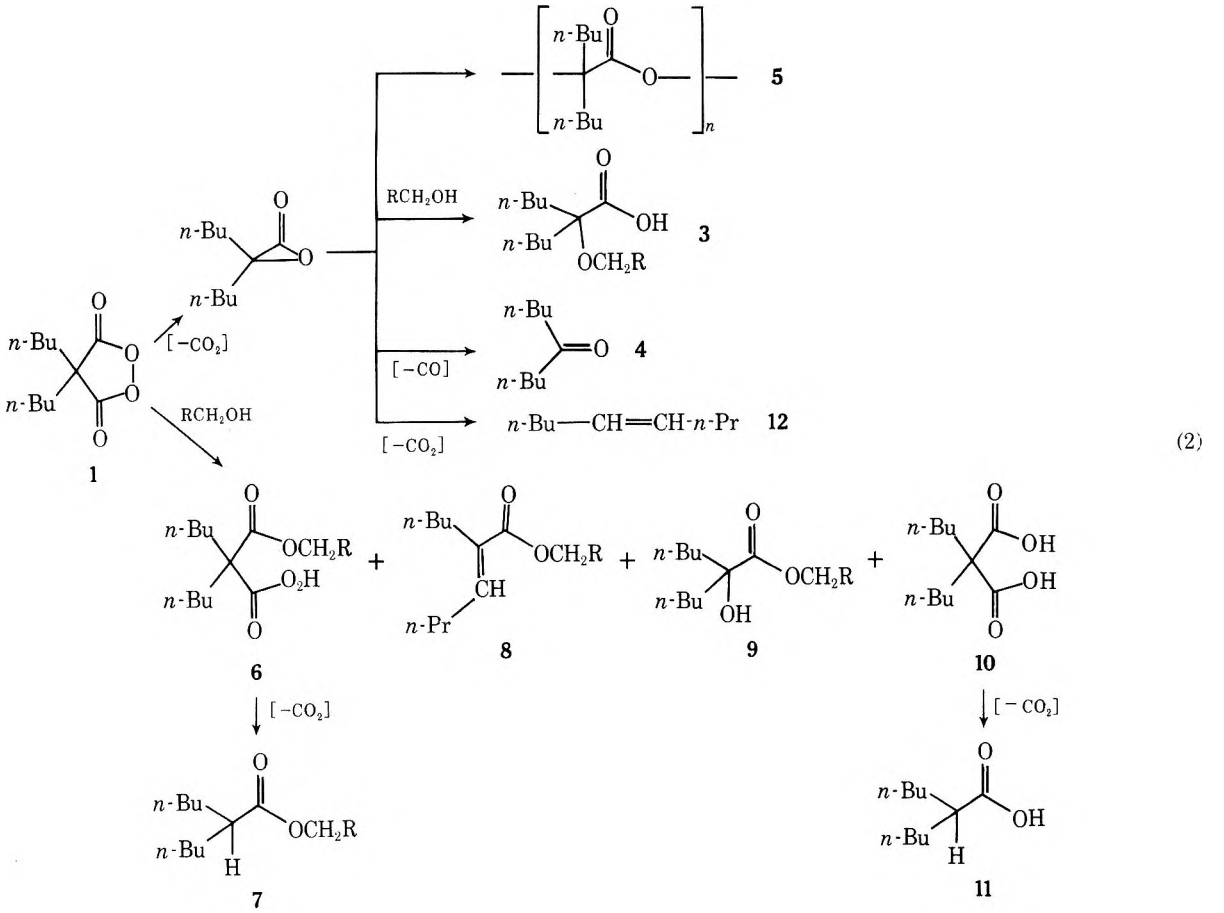
VPC analysis of the solvent distillate showed that the only volatile products were 5-nonanone (**4**) and 4-nonene (**12**). The quantitative product data of the photolysis are summarized in Table I. Control experiments revealed that the polyester **5** was stable toward irradiation at 350 nm under the reaction conditions. Thus, the 5-nonanone (**4**) and 4-nonene (**12**) are not secondary photolysis products but must arise directly on photolysis of the malonyl peroxide **1**. However, irradiation of a 0.1 M polyester solution in *n*-hexane at 254 nm for 63 h in a quartz vessel led to ca. 60% deterioration of the polyester **5** leading principally to ketone **4**, but it is important to note that under these conditions the malonyl peroxide is completely destroyed within 40 min on irradiation at 254 nm in a quartz vessel.

In contrast to the ease with which the malonyl peroxide **1** photodecarboxylates, it is thermally quite stable in inert solvents such as benzene or *n*-hexane. Thus, a 0.10–0.15 M solution of **1** in these solvents must be heated at 140 °C for 5–6 h in sealed ampules to effect complete destruction. Again, the major product is the polyester **5**, formed in 85–91% yield (Table II). The remainder are volatile products, mainly the unsaturated acid **8** (isolated as its methyl ester for convenience of VPC analysis, cf. Experimental Section) and 5-nonanone. In the case of *n*-hexane as the reaction solvent, appreciable amounts of carboxylic acid **11** were also detected (also isolated as its methyl ester for convenience of VPC analysis, cf. Experimental Section). The quantitative results of the relative composition (by VPC) of the volatile products are summarized in Table II as well as the gravimetric absolute yields of polyester **5**.

A control experiment confirmed that on heating at 230 °C for 1 h in benzene the polyester **5** is converted essentially quantitatively into the α,β-unsaturated acid **8**. Consequently, the major component of the volatile products, i.e., acid **8**, presumably arises from subsequent thermal destruction of the polyester **5**.

Clearly, both in the photolysis and the thermolysis of the malonyl peroxide **1** the α-lactone **2** intervenes as precursor to the polyester **5**. Thus, if the α-lactone intermediate is long lived enough to polymerize, it should be possible to trap it with protic solvents such as alcohol. Consequently, we examined the photolysis and thermolysis of the malonyl peroxide **1** in methanol and ethanol.

The photolysis results in methanol and ethanol are given in Table I. First of all, as expected the yield of polyester **5** is dramatically reduced; the α-alkoxy acid **3** is formed as the major product by nucleophilic trapping of the α-lactone intermediate with the alcohol solvent. Some 5-nonanone (**4**) and traces of 4-nonene (**12**) are also produced. The remainder of the products, i.e., half-ester **6**, ester **7**, α,β-unsaturated ester **8**, α-hydroxy ester **9**, malonic acid **10**, and acid **11**, all together representing less than 10% of the volatile products, are derived from competitive solvent-induced reaction of the malonyl peroxide.[7] Except for this minor side reaction, the photodecarboxylation in these alcoholic solvents is quite clean, leading to the solvent-trapped α-lactone as the final major product. As Table I reveals, the relative product composition is quite insensitive to the type of alcohol used (MeOH vs. EtOH) and wavelength (350 vs. 310 nm). Control experiments confirmed that the polyester **5** was solvolytically and photolytically stable



(2)

under the reaction conditions. Furthermore, the major product, i.e., the α-alkoxy acid **3**, was also inert to the photolysis conditions.

The thermolysis results, which are given in Table II, of the decomposition of the malonyl peroxide in the alcoholic solvents are considerably more complex than the photolysis. In methanol, considerable amounts of polyester **5** are still formed, but the major product is the α-methoxy acid **3**, resulting from methanol trapping of the α-lactone **2** intermediate. Only traces of 5-nonanone and 4-nonene are formed. The remainder of the products are derived from solvent-induced decomposition of the malonyl peroxide **1**.[7] Control experiments show that the malonic acid **10** decarboxylates to give acid **11**, and the half-ester **6** similarly decorboxylates to give ester **7** under the reaction conditions. However, the α-alkoxy acids **3** are stable to the reaction conditions and, thus, are not a source for the secondary products. Consequently, in methanol the major course of the thermolysis is α-lactone formation, but methanol-induced decomposition of the malonyl peroxide **1** competes effectively.

A contrary situation obtains in ethanol (Table II). First of all, relatively little polyester **5** is produced on thermolysis of malonyl peroxide **1** in ethanol. Furthermore, among the volatile products, the α-ethoxy acid **3** (ethanol trapping of α-lactone **2**) is formed only in ca. 18% yield. Again only traces of 5-nonanone (**4**) are produced.

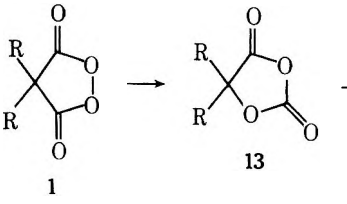
The major products are the acid **11** and ester **7**, both arising from decarboxylation of the malonic acid **10** and half-ester **6**, which in turn are derived from ethanol-induced decomposition of **1**.[7] Thus, in ethanol the major event is solvolytic destruction of the malonyl peroxide **1** rather than α-lactone formation. The greater propensity of ethanol to become engaged in radical chain reactions compared to methanol is clearly evident in these results.[9]

A unified mechanism accounting for these results is offered in eq 2. The lower branch, i.e., the solvolytic reaction by methanol or ethanol affording products **6** to **11**, has already been interpreted mechanistically[7] and shall, therefore, not be discussed here any further. For convenience, we have retained the same numbering sequence of the solvolytic products as given in reference 7 to facilitate comparison.

The upper branch proceeding through the α-lactone intermediate is the exclusive path in the photolysis and thermolysis of the malonyl peroxide **1** in nonprotic solvents such as benzene and *n*-hexane. Most of the α-lactone **2** polymerizes to afford the polyester **5**, some decarbonylates into 5-nonanone, and presumably a little decarboxylates to give 4-nonene via the corresponding carbene.[4-6]

Also photolysis in methanol or ethanol affords principally the α-lactone **2**, which now, however, is trapped by the protic solvent through its dipolar form **2a** as the α-alkoxy acid **3**. Even then some of the α-lactone manages to polymerize and decarbonylate but very little decarboxylates, since only traces of 4-nonene are formed. The solvolytic pathway (lower branch in eq 2) occurs to a minor extent (less than 10%) in these photolyses. However, in the thermolysis reaction of malonyl peroxide **1** in these alcoholic solvents the solvolytic process competes effectively. For methanol, the major path is still α-lactone formation, but for ethanol the major path is solvolysis.

The possibility, although quite improbable, that the malonyl peroxide **1** carboxy inverts[10] to give the isomeric 1,3-dioxolane-2,4-dione (**13**) (eq 3) and the latter then serves as a precursor to the α-lactone products was discounted by the



(3)

following control experiment. Authentic 5,5-dimethyl-1,3-dioxolane-2,4-dione (**13a**) was prepared[11] and shown to be stable to the photodecarboxylation conditions of the malonyl peroxide **1**. The anhydrocarbonate **13a** could be destroyed by irradiating with a full mercury arc of a 200-W Hanovia lamp in acetonitrile using a quartz reaction vessel (Corex filtter). Acetone and ca. 10% tarry residue were the only products. Thermolysis in benzene, as reported previously,[11] leads to polyester, presumably via an α-lactone intermediate.

Experimental Section

Instruments. Infrared spectra were recorded on a Perkin-Elmer Infracord 237-B using 0.1-mm sodium chloride cavity cells, and the absorptions are given in reciprocal centimeters. The NMR spectra were recorded on a Varian T-60 spectrometer using normal and semimicro NMR tubes. The chemical shifts are given in δ (ppm) using Me_4Si as an internal standard. The VPC analyses were carried out on a Varian Aerograph 202-B instrument, provided with TC detection, employing the following columns under the conditions specified below.

Condition CX-1: 5 ft × 0.25 in. copper column, packed with 15% Carbowax 20 M on 60–80 mesh Chromosorb W, operated at column, injector, and detector temperatures of 155, 200, and 250 °C, respectively, and a helium flow of 60 mL/min.

Condition CX-2: 15 ft × 0.25 in. copper column, packed with 20% Carbowax 20 M on 60–80 mesh Chromosorb W, operated at column, injector, and detector temperatures of 175, 225, and 250 °C, respectively, and a helium flow of 60 mL/min.

Conditions AZ-1: 12 ft × 0.25 in. copper column, packed with 27% Apiezon M on 60–80 mesh Chromosorb P, operated at column, injector, and detector temperatures of 210, 225, and 250 °C, respectively, and a helium flow of 60 mL/min.

Conditions AZ-2: 12 ft × 0.25 in. copper column, packed with 18% Apiezon M on 60–80 mesh Chromosorb P, operated at column, injector, and detector temperatures of 205, 225, and 250 °C, respectively, and a helium flow of 60 mL/min.

Chemicals. All commercial solvents and reagents were purified according to literature methods to match reported physical constants. All the starting materials and products were prepared according to published literature procedures and purified to match the reported physical constants. The details will not be reproduced here, since the substances 2-*n*-butyl-2-ethoxyhexanoic acid, 2-*n*-butylhexanoic acid, 2-*n*-butyl-2-methoxyhexanoic acid, di-*n*-butylmalonic acid, di-*n*-butylmalonyl peroxide, diethyl di-*n*-butylmalonate, dimethyl di-*n*-butylmalonate, ethyl 2-*n*-butylhexanoate, ethyl *cis,trans*-2-*n*-butyl-2-hexenoate, ethyl 2-*n*-butyl-2-hydroxyhexanoate, ethyl 2-*n*-butyl-2-methoxyhexanoate, ethyl hydrogen di-*n*-butylmalonate, ethyl methyl di-*n*-butylmalonate, hydrogen methyl di-*n*-butylmalonate, methyl 2-*n*-butyl-2-ethoxyhexanoate, methyl 2-*n*-butylhexanoate, methyl *cis,trans*-2-*n*-butyl-2-hexenoate, methyl 2-*n*-butyl-2-hydroxyhexenoate, methyl 2-*n*-butyl-2-methoxyhexanoate, and 5-nonanone are described in reference 7, 2-*n*-butyl-1,2-hexanediol in reference 8, and 5,5-dimethyl-1,3-dioxolane-2,4-dione in reference 11.

General Photolysis and Thermolysis Procedures. A stock solution of the malonyl peroxide was prepared in the desired anhydrous solvent at the appropriate concentration (~0.3 M), distributed into constricted Pyrex test tubes, and sealed under vacuum. In the case of photolyses, these ampules were placed into the RP-100 Rayonet Photoreactor, equipped with a merry-go-round and the appropriate lamps, and photolyzed at 35–40 °C. In the case of thermolyses, these ampules were placed into a constant-temperature bath, which was regulated at the desired temperature within ±1.0 °C. When the peroxide titer had dropped below 0.5%, as determined by iodometric titration of samples taken periodically, the remaining ampules were opened, and the contents were combined and treated with an ethereal solution of diazoalkane (diazomethane in the case of ethanol, benzene and *n*-hexane and diazoethane in the case of methanol as solvent) until persistence of the yellow color. The solvent was removed at reduced pressure, collecting the distillate in a dry ice cooled vacuum trap, concentrating the reaction mixture to 2–3 mL volume. The residual oily product was bulb-to-bulb distilled at reduced pressure (130–140 °C at 0.05 mm), flushing several times with 3–5 mL of solvent distillate. The yield of involatile residue, identified as polyester as described below, was determined gravimetrically. The molecular distillate and the solvent distillate were combined, adjusted to the appropriate volume, and submitted to VPC analysis using conditions CX-2 and AZ-1. Each product formed in amounts greater than 0.1 mol % was collected, and its structure was confirmed by comparison of VPC retention times and IR and ^1H NMR spectra with authentic materials. The quantitative VPC results are reported in Table I for the photolyses and Table II for the thermolyses as relative compositions (mol %) of the volatile products and absolute yields (wt %) of involatile residue; nearly 100% product balance was achieved in most runs.

Characterization of Polyester 5. The involatile residue, obtained after removal of the solvent and the volatile products, consisted of a partly crystalline, colorless powder, mp 138.5–140.5 (benzene) and 146.0–146.5 °C (*n*-hexane). This residue was identified as polyester **5** [poly(3,3-di-*n*-butyloxiran-2-one)] on the basis of its elemental analysis, its molecular weight of 4996 (osmometry in $CHCl_3$), corresponding to 29.2 α-lactone units, its C=O band at 1740, and lithium aluminum hydride reduction to 2-*n*-butylhexane-1,2-diol in 72% yield after distillation, bp 110 °C at 0.3 mm, n^{20}_D 1.4527 (lit.[8] bp 140 °C at 13 mm, n^{20}_D 1.4538).

Solvolytic Stability of Polyester 5 in Methanol. A 0.1 M solution of the polyester in benzene and methanol (5:1) was irradiated at 350 nm in a Pyrex test tube for 17 h. By means of IR analysis it was established that no 2-*n*-butyl-2-methoxyhexanoic acid (**3**, RCH_2 = methyl) was formed.

Photolytic Stability of Polyester 5 in Hexane. A 0.1 M solution of **5** in hexane was irradiated at 350 nm for 45 h in a Pyrex test tube. By IR analysis, not even traces of ketone **4** or olefin **12** were formed. However, irradiation of a 0.1 M hexane solution of **5** in a quartz vessel at 254 nm for 63 h indicated that 60% deterioration of the polyester had taken place to give principally ketone **4**.

Thermal Stability of Polyester 5. A 0.1 M solution of polyester **5** in benzene which was heated in an ampule at 230 °C for 1 h was converted quantitatively into the α,β-unsaturated acid **8**, as confirmed by IR analysis.

Photolysis of Malonyl Peroxide 1 at 254 nm in Hexane. When a 0.1 M hexane solution of **1** was irradiated at 254 nm in a quartz vessel at −78 °C, within 40 min all peroxide was consumed, as confirmed by monitoring the reaction mixture by IR. Polyester **5** was formed essentially quantitatively.

Photolysis of Malonyl Peroxide 1 in the Absence and Presence of Molecular Oxygen. A 0.1 M stock solution of **1** in benzene was divided into two equal portions and placed into constricted Pyrex test tubes by means of a syringe. One sample was rigorously deaerated with helium gas using five freeze–pump–thaw cycles and sealed under vacuum; the other sample was saturated with molecular oxygen using five freeze–pump–thaw cycles and sealed at atmospheric pressure. Both ampules were irradiated at 350 nm in the RP-100 Rayonett photoreactor until complete consumption of peroxide (no 1783 band in the IR). Each ampule was opened, and the solvent was removed at reduced pressure, collecting it in a dry ice vacuum trap, and analyzed for 5-nonanone by IR and VPC. No significant differences in yield could be discerned between the two samples.

Photolysis of 5,5-Dimethyl-1,3-dioxolane-2,4-dione (13). A 0.1 M solution of the 1,3-dioxolane **13** in benzene was irradiated in a Pyrex ampule at 310 nm. Even after 75 h no consumption of 1,3-dioxolane **13** was observed. However, irradiation of a 0.1 M solution in acetonitrile with a 200-W Hanovia lamp, filtering with a Corex filter, gave acetone as the only product after 21.5 h of irradiation.

Photolytic Stability of 2-*n*-Butyl-2-methoxyhexanoic Acid (3). A 0.1 M methanolic solution of the α-methoxy acid **3** in a Pyrex test tube was irradiated at 350 nm for 24 h. Treatment of the resulting solution with excess diazomethane and submission to VPC analysis (conditions CX-1) confirmed that not even traces of ketone **4** or α,β-unsaturated ester **8** were formed. The exclusive product was the α-methoxy acid **3** in the form of its methyl ester.

Thermal Stability of 2-Alkoxy-2-*n*-butylhexanoic Acid (3). A 0.30 M solution of the α-alkoxy acid **3** (RCH_2 methyl or ethyl) in the appropriate alcohol (methanol or ethanol) was heated in an ampule for 2 h at 140 °C, esterified with the appropriate diazoalkane, and analyzed by VPC (conditions AZ-1 and CX-2). The α-alkoxy acid was stable under these thermolysis conditions.

Thermal Stability of Di-*n*-butylmalonic Acid (10). A 0.30 M solution of the malonic acid **10** in the alcohol (methanol or ethanol) was heated in an ampule at 130 °C for 2 h. The mixture was then esterified with the appropriate diazoalkane (diazoethane in the case of methanol and diazomethane in the case of ethanol) and analyzed by VPC (conditions CX-2). In both solvents a total of 92–92.5% decarboxylation took place to give 2-*n*-butylhexanoic acid (**11**), while the remainder 7.5–8.0% was converted to the dialkyl malonate (dimethyl in the case of methanol and diethyl in the case of ethanol).

Thermal Stability of Alkyl Hydrogen Di-n-butylmalonate (6). A 0.3 M solution of the half ester **6** (RCH_2 methyl or ethanol) in al-

cohol (methanol or ethanol) was heated in an ampule at 140 °C for 2 h. The mixture was then esterified with the appropriate diazoalkane (diazoethane in the case of methanol and diazomethane in the case of ethanol) and analyzed by VPC (conditions AZ-1). In both solvents about 33–34% of decarboxylation took place to give alkyl 2-*n*-butylhexanoate (7).

Acknowledgments are made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation (Grant CHE-77-13308), and the National Institutes of Health (Grants GM-22119-02, GM-00141-02, and RR-8102-03) for support of this work.

Registry No.—**1**, 30842-78-5; **3** (R = H), 36602-15-0; **3** (R = Me), 36602-18-3; **4**, 502-56-7; **5**, 67315-53-1; *cis*-8 ($RCH_2 = CH_3$), 36602-24-1; *trans*-8 ($RCH_2 = CH_3$), 36602-25-2; **11**, 3115-28-4; 13 (R = Me), 22713-42-4; di-*n*-butylmalonic acid, 2283-16-1.

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Rearrangement of Allyl Alcohols to Aldehydes with Superacids[1]

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The superacid-catalyzed rearrangement of allyl alcohols into aldehydes was studied in superacid solutions under stable ion conditions followed by ^1H NMR spectroscopy, as well as in the gas phase over a solid perfluorinated resinsulfonic acid catalyst (Nafion-H).

The catalytic rearrangement of allyl alcohol to propionaldehyde, brought about by H_2SO_4,[2] $Fe(CO)_4$,[3] $Fe(CO)_5$,[4] $Co_2(CO)_8$,[5] and acid-catalyzed electrolysis,[6] as well as in the gas phase, over Al_2O_3, ZnO, or pumice at elevated temperatures[7] has been studied. We wish to report now a study of the mechanism of the superacid-catalyzed isomerization of allyl alcohols in superacid solutions under stable ion conditions using ^1H NMR spectroscopy and directly observing the intermediate(s) responsible for such transformations. We also report that similar superacid-catalyzed isomerization takes place by catalysis over Nafion-H, a solid perfluorinated resinsulfonic acid in the gas phase at relatively mild conditions. Allyl alcohol is effectively isomerized to propionaldehyde. 2-Methylallyl alcohol, crotyl alcohol, and 3-methyl-2-buten-2-ol are also isomerized, under the same condition, to isobutyraldehyde, butyraldehyde and methyl isopropyl ketone, respectively.

Study of Allyl Alcohols in Superacid Solutions

When a solution of allyl alcohol **1** in SO_2ClF at −78 °C (dry ice–acetone bath) is slowly introduced into a well-stirred solution of FSO_3H–SbF_5–SO_2ClF kept below −100 °C (ethanol–dry ice bath), protonated allyl alcohol **2** is observed.

$$\underset{\textbf{1a, R = H}\\ \textbf{b, R = CH}_3}{RCH{=}CHCH_2OH} \xrightarrow[<-100\ ^\circ C]{FSO_3H\text{–}SbF_5\text{–}SO_2ClF} \underset{\textbf{2a, R = H}\\ \textbf{b, R = CH}_3}{RCH{=}CHCH_2OH_2^+} \quad (1)$$

The structure of **2** is identified by its 60-MHz ^1H NMR spectrum (Figure 1) obtained at −90 °C, which shows four proton resonances (Table I). The two-proton signal at δ 9.75 assigned to the protonated hydroxyl group confirms the formation of **2**. Protonated alcohols are known to show strong absorptions at about δ 10–11 in superacids.[8]

When raising the temperature of protonated allyl alcohol **2** in FSO_3H–SbF_5–SO_2ClF above −80 °C, **2** slowly undergoes addition of FSO_3H to the double bond, giving protonated 2-fluorosulfonyl-1-propanol (**3**). The structure of **3** is confirmed by its proton and fluorine-19 NMR spectra (Table I). The process of slow transformation from **2** (−90 °C) to **3** (−40 °C) is clearly seen in Figure 1. When the solution of **2** is allowed to stand at −40 °C, the original ^1H NMR spectrum *of*

Table I. Proton and Fluorine-19 NMR Parameters of Protonated Allyl Alcohol and Its FSO_3H and HF Addition Products

ion	registry no.	acid (temp, °C)[b]	CH_3	CH_2–OH_2^+	CH	=CH	$=CH_2$	$-CH_2-$	OH_2^+	ϕ_{19F}	$J_{H\text{-}F}$, Hz
2	67315-77-9	A, B, (−90)		5.28 (d, 6.0)		6.58 (m)	6.17 (m)		9.75 (b)		
3a	67315-78-0	A (−50)	185 (d, 6.6)	5.12 (b)	5.78 (m)				11.05 (b)	−40.0 (s)	
3b	67315-79-1	A (−50)	1.94 (t)	5.24 (b)	5.75 (b)			3.88 (m)	10.3		
4	67315-80-4	B (−50)	1.60 (dd, 6.6)	5.10 (dt)	5.75 (dqm)				11.0 (t, 4.0)	+185.3 (dq)	$J_{CH_3\text{-}F}$ = 24.0; $J_{CH_2\text{-}F}$ = 22.0; $J_{CH\text{-}F}$ = 50.0

[a] Proton and fluorine-19 chemical shifts are in ppm from external Me_4Si and CCl_3F, respectively. Multiplicities and coupling constants (in Hz) are given in parentheses: b = broad, d = doublet, m = multiplet, s = singlet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, dqm = doublet of quartet of multiplets, tt = triplet of triplets, td = triplet of doublets, qt = quartet of triplets. [b] A = FSO_3H–SbF_5–SO_2ClF; B = HF–SbF_5–SO_2ClF.

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2 is completely replaced by that of 3. In order to further establish the reaction of 2a in $FSO_3HSbF_5SO_2ClF$, we have also treated allyl alcohol with $HFSbF_5SO_2ClF$ under the same conditions.

$RCH_2C(X)HCH_2OH_2^+$

3a, X = OSO_2F; R = H

b, X = OSO_2F; R = CH_3

4, X = F; R = H

According to the ^1H NMR spectra of the solution of 1 in this acid system, both the protonation of the hydroxy group (2) and the addition of HF to the double bond (to give protonated 2-fluoro-1-propanol (4)) take place at −90 and −78 °C, respectively. The structure of 4 is characterized inter alia by the large J_{H-F} coupling and fluorine-19 resonance (Table I). Brouwer et al.[9] reported that addition products of the acid solvent ($HF:SbF_5$ or $HSO_3F:SbF_5$) to 3-penten-2-one and analogues are serving as intermediates in the cyclization process of these compounds to tetrahydrofuran derivatives via a multistep reaction.

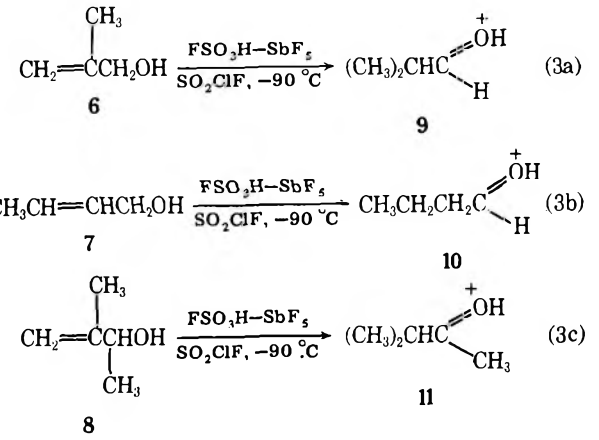
In the presently discussed cases, the addition products between the acid (HF or HSO_3F) and the protonated allyl alcohols 3 and 4 cannot play a role in the reaction mechanism as they would prevent further reaction, i.e., the 1,2-hydride shift to give the protonated carbonyl compound. Hence, the reaction rate at this stage is controlled by the elimination of the acid from 3 or 4.

The thermal stability of 3 and 4 is different. The solution of 4 in $HF–SbF_5–SO_2ClF$ undergoes no further change when the temperature is raised from −78 to 0 °C (pressure NMR tube). In contrast, a slow transformation yielding protonated propionaldehyde (5)[10] takes place when the solution of 3 in $FSO_3H–SbF_5–SO_2ClF$ is allowed above − 40 °C (Figure 1, eq 2).

$$CH_2{=}CHCH_2OH_2^+ \overset{HX}{\rightleftharpoons} CH_3C(X)HCH_2OH_2^+ \overset{-HX}{\rightleftharpoons} [CH_3CH^+CH_2OH] \xrightarrow{1,2\text{-H}} \underset{5}{CH_3CH_2CHOH^+} \quad (2)$$

The ^1H NMR spectrum of 5 (recorded after the solution has been cooled back to −80 °C) is identical to that previously reported for protonated propionaldehyde.[10] The proton spectrum of 5 displayed in Figure 1 at 0 °C indicates fast exchange between the proton on oxygen and the acid (FSO_3H). The difference in reactivity between 3 and 4 reflects the difference in C–X bonds, i.e., the C–O(SO_2F) bond is weaker than the C–F bond.

2-Methylallyl alcohol (6), crotyl alcohol (7), and 2,3-dimethylallyl alcohol (8) also undergo similar isomerization in $FSO_3H–SbF_5–SO_2ClF$ solution yielding protonated isobutyraldehyde (9)[10] (eq 3a), protonated butyraldehyde (10) (eq 3b), and protonated methyl isopropyl ketone (11)[11] (eq 3c), respectively. The ^1H NMR spectra of 9–11 are identical to those previously reported.[10,11]



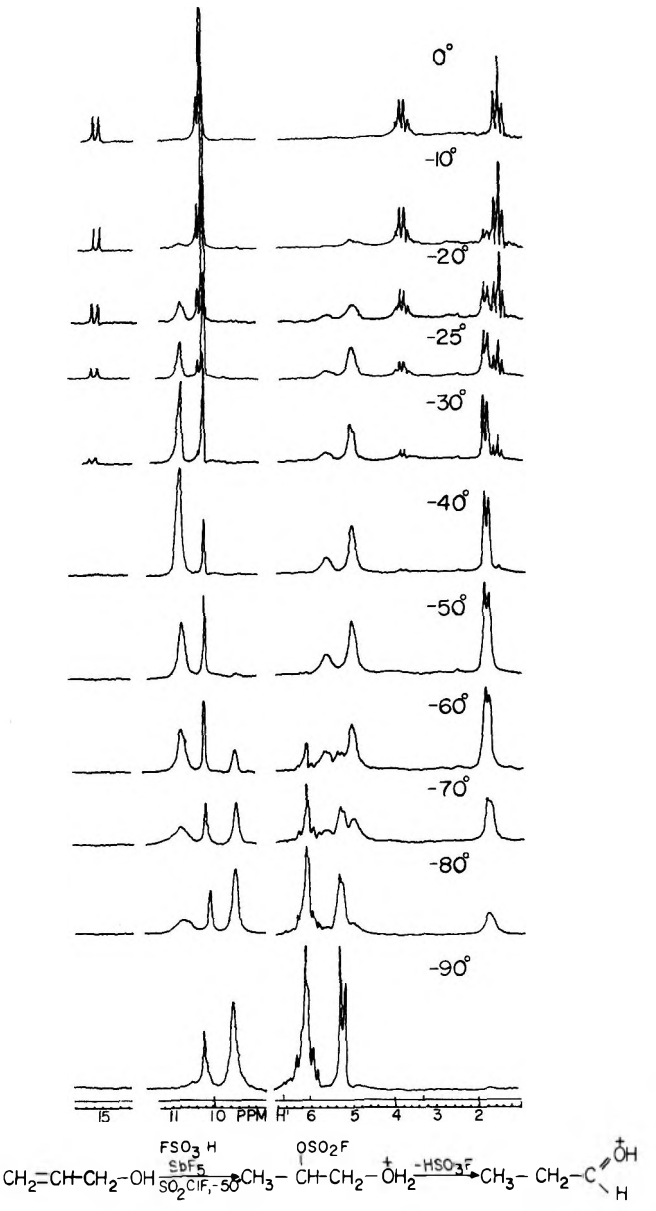
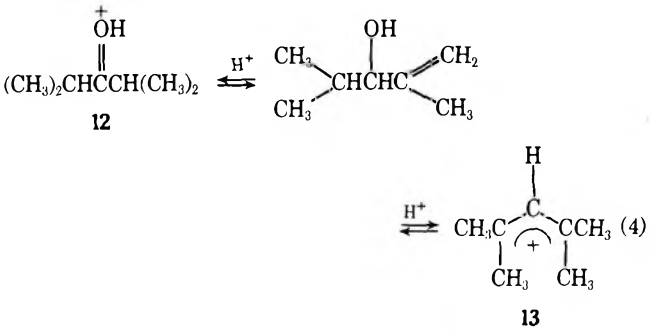


Figure 1.

We have previously[12] reported our results on the formation of allyl cations from the corresponding allylic alcohol in superacidic media. Ionization of 2,4-dimethyl-1-penten-3-ol gave a 1:1 mixture of 12 and 13 (eq 4). In treating alcohols 1 and

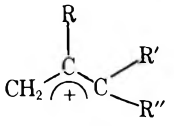


6–8 in superacids under similar conditions, no ionization of the OH_2^+ group takes place to give the corresponding allyl cations 14–16. The results are in agreement with the findings

Table II. Isomerization of Allylic Alcohols to Aldehydes in the Gas Phase over Nafion-H Catalyst[a]

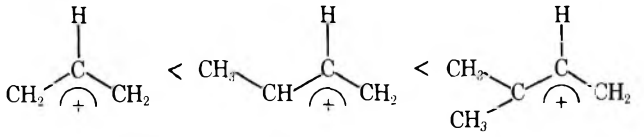
alcohol	registry no.	reaction temp, °C	liquid feed rate, mL/min	contact time, s	product (aldehyde yield, %)	registry no.
Allyl	107-18-6	195	0.06	3	propionaldehyde (40)	123-38-6
		195	0.02	8	(60)	
		170	0.02	8	(45)	
		140	0.02	8	(0)	
2-Methylallyl	513-42-8	195	0.06	3	isobutyraldehyde (88)	78-84-2
		180	0.06	3	(80)	
Crotyl	6117-91-5	195	0.02	8	butyraldehyde (55)	123-72-8
		195	0.06	3	(40)	

[a] Carrier gas, nitrogen at 30 mL/min.

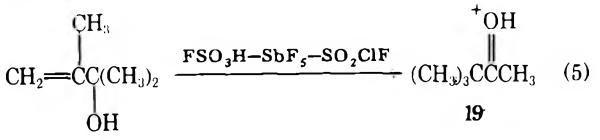


14, R = R′ = R″ = H
15, R = R″ = H; R′ = CH_3
16, R = R′ = CH_3; R″ = H
17, R = R′ = R″ = CH_3

indicating that the stabilities of allylic cations are in the order:



The same order was observed in solvolytic rate studies of the corresponding allyl chlorides[13] indicating that the addition of a methyl group to a terminal carbon in the allylic ion stabilizes it by ~5 kcal/mol. Addition of the tertiary 2,3,3-trimethylallyl alcohol **18** into FSO_3H–SbF_5–SO_2ClF solution at −90 °C gave only the isomerized product, i.e., methyl *tert*-butyl ketone **19** (protonated) (eq 5), and the allylic ion **17** was not detected.



(5)

18 **19**

The Rearrangement of Allyl Alcohols over Nafion-H Catalyst in the Gas Phase

When gaseous allyl alcohols were passed over Nafion-H, a polyfluorinated resinsulfonic acid, at 170–190 °C, rearrangement occurred giving the corresponding aldehydes. Table II summarizes the data obtained from the rearrangement of allyl and substituted allyl alcohols in the gas phase over the solid superacidic catalyst. The reactions are substantially influenced by the temperature as well as by the contact time. The data suggest that reaction occurs faster with 2-methylallyl alcohol than with allyl or crotyl alcohols. This is in agreement with the mechanism, discussed earlier herein.

Experimental Section

Materials. Allyl alcohols used are commercially available.

NMR Spectra. A Varian Associates Model A-56/60A spectrometer with variable temperature probe was used for all spectra. Chemical shifts are recorded in ppm (δ) from external (capillary) Me_4Si for ^1H NMR spectra and from external (capillary) CCl_3F for ^{19}F NMR spectra.

Study of the Rearrangement of Allyl Alcohols in Superacid Solution. The procedure used for the preparation of FSO_3H–SbF_5–SO_2ClF and HF–SbF_5–SO_2ClF solutions of the protonated alcohols was the same with that described earlier.[11]

Solutions of the protonated alcohols were prepared by dissolving the appropriate precursors (approximately 0.1 mL) in 0.5 mL of SO_2ClF at the desired temperature and slowly adding the mixture to a well-stirred solution of 1 mL of FSO_3HSbF_5 or HF–SbF_5 solutions (1:1 molar solutions) in 1 mL of SO_2ClF maintained at dry ice–acetone bath temperature. (Dry ice ether slug was used for protonation at temperatures lower than −90 °C.) The resulting solution was transferred immediately with cooling into an NMR tube precooled at dry ice–acetone temperature.

Rearrangement of Allyl Alcohols in the Gas Phase over Nafion-H Catalyst. The reactor, experimental procedure, and activation of Nafion-H catalyst were those previously reported.[14] Reactions were carried out at temperatures between 140 and 195 °C, using 1 g of the catalyst. Products were collected in a trap immersed in a −60 °C bath. Products were identified using IR and NMR spectroscopies.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

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Electronic Structure of Tetraphenylthieno[3,4-c]thiophene. Photoelectron, Electron Spin Resonance, and Electronic Absorption Spectra[1]

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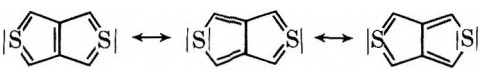
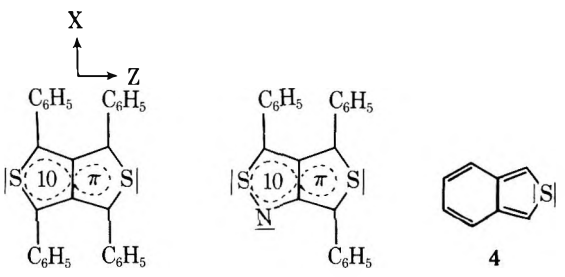
The He I photoelectron (PE) spectrum of tetraphenylthieno[3,4-c]thiophene (2) has been reassigned by comparison with the PE spectrum of 1-azatriphenylthieno[3,4-c]thiophene (3) and orbital energies obtained by extended Hückel calculations on 2. The radical anion and cation of 2 and the radical anion of benzoisothiophene (4) have been generated and the hyperfine splitting in their ESR spectra has been completely analyzed. The linear dichroism of the most intense bands in the electronic absorption spectrum of 2 has been measured. An assignment of the first bands in the absorption spectrum of 2 is given based on a comparison with results of PPP–CI calculations. All data measured can be rationalized by a MO model, which generates the "nonclassical" thienothiophene π system by perturbation of the parent pentalene.

The nature of bonding in the "nonclassical" condensed thiophenes still remains a matter of controversy.[6] The parent molecule thieno[3,4-c]thiophene (1), which has so far escaped



1a 1b 1c

isolation, "is expected to be more aromatic than two thiophene molecules",[7] and the photoelectron spectrum of its stable tetraphenyl derivative 2 has been assigned by simply neglecting the phenyl groups.[7] Nevertheless, molecular orbital models proposed[7-9] for the interesting 10 π-electron system of 1 should be useful, if appropriately applied[10] in rationalizing the properties of the individual molecular states of stable derivatives. In the following, photoelectron (PE), electron spin resonance (ESR), and electronic absorption data for 2 and the



2 3 4

related compounds 1-azatriphenylthieno[3,4-c]thiophene (3) and isobenzothiophene (4) or their radical ions, respectively, are reported and discussed.

I. PE Spectra

The PE spectra of 2 and 3 have been reported previously.[7,11] In Figure 1 our assignment for the low-energy region of both spectra is summarized, based on the validity of Koopmans' theorem[12] ($-\epsilon_j = I_{V,j}$).

The two PE spectra display several similarities. A first peak at low ionization energy is separated by a large gap from a second one, which is close to a very intense third one. To label the molecular orbitals of the aryl derivatives 2 and 3 we use the irreducible representations of the D_{2h} group, although X-ray investigations on 2 reveal[13] that its phenyl groups are twisted by 39.6 and 58.4° out of the molecular plane. Also for the aza derivative D_{2h} symmetry is not preserved any more.

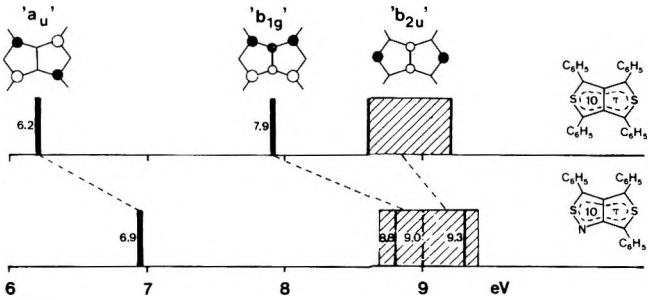


Figure 1. Comparison between the first bands of the PE spectra of 2 and 3.

Our assignment for the PE bands of 2 is different from that proposed in the literature[7] insofar as our extended Hückel (EH)[14] calculations on 2, which include the phenyl groups, predict the orbital sequence $a_u < b_{1g} < b_{2u}$ as shown in Figure 1. This reversed sequence with b_{1g} on top of b_{2u} is due to interaction of σ orbitals of the phenyl rings with the b_{1g} orbital of the thieno[3,4-c]thiophene fragment, being strong for a_u and b_{1g} but relatively small for b_{2u}.

The revised assignment is corroborated by the comparison between the PE spectra of 2 and 3 as displayed in Figure 1. Aza substitution causes a strong shift toward higher ionization energy for the first two bands, but not for the one assigned to b_{2u}. This is exactly what one expects from first-order perturbation theory[16] by π-isoelectronic replacement of one C-C_6H_5 unit by a more electronegative nitrogen atom.

II. ESR Spectra of 2^+ and 2^-

Information on the shape of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) is provided by the ESR spectra of the radical cation 2^+ and the radical anion 2^-. These have been generated by treating a solution of 2 in methylene chloride with $AlCl_3$ or $AgBF_4$ or a solution of 2 in dimethoxyethane with K, respectively. For comparison also 4 has been reduced to 4^-.

The ESR spectra of 2^+, 2^-, and 4^- (Figures 2a–4a) are best reproduced by computer simulation with the assigned coupling constants (Figures 2b–4b). The hyperfine coupling constants obtained by the correlation are listed in Table I, which also contains calculated spin densities according to McLachlan[17] and calculated coupling constants according to Karplus and Fraenkel.[18]

The ESR spectrum of 2^+ comprises 21 lines. It can be re-

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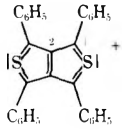
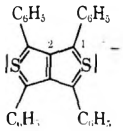
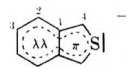
Table I. ESR Data for 2^+, 2^-, and 4^-: Calculated Spin Densities and Coupling Constants

	registry no.	μ	$a_{X,\mu}^{exp}$, mT	ρ_μ^{HMO}	$a_{X,\mu}^{calcd}$, mT	g
	67124-76-9	1	1.146	0.316	1.128[a]	
		2		−0.074		
		S		−0.057		2.0020
		H_o	0.044[b]			
		H_m	0.044			
		H_p	0.132			
	67179-20-8	1		0.231		
		2		−0.062		
		S		0.099		2.0056
		H_o	0.069[b,c]			
		H_m	0.069			
		H_p	0.095			
	35131-96-5	1		−0.060		
		H_2	0.435	0.203	0.508	
		H_3	0.284	0.030	0.075[d]	2.0039
		H_4	0.490	0.276	0.690	
		S		0.114		

[a] According to Karplus–Fraenkel[18] with $Q_C = 3.1$, $Q_{CC} = 1.4$, and $Q_{SC} = -0.8$ mT. [b] Assumed for simulation to be confirmed by ENDOR. [c] Strongly temperature dependent. [d] $Q_{CH} = -2.5$ mT.

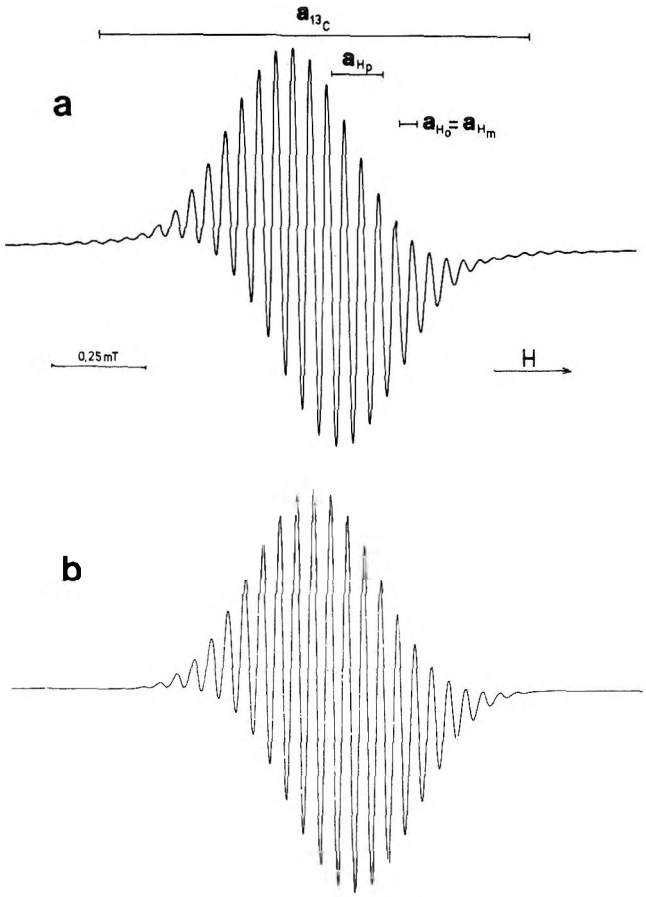


Figure 2. (a) ESR spectrum of 2^+ in CH_2Cl_2 at 200 K. (b) Computer simulation.

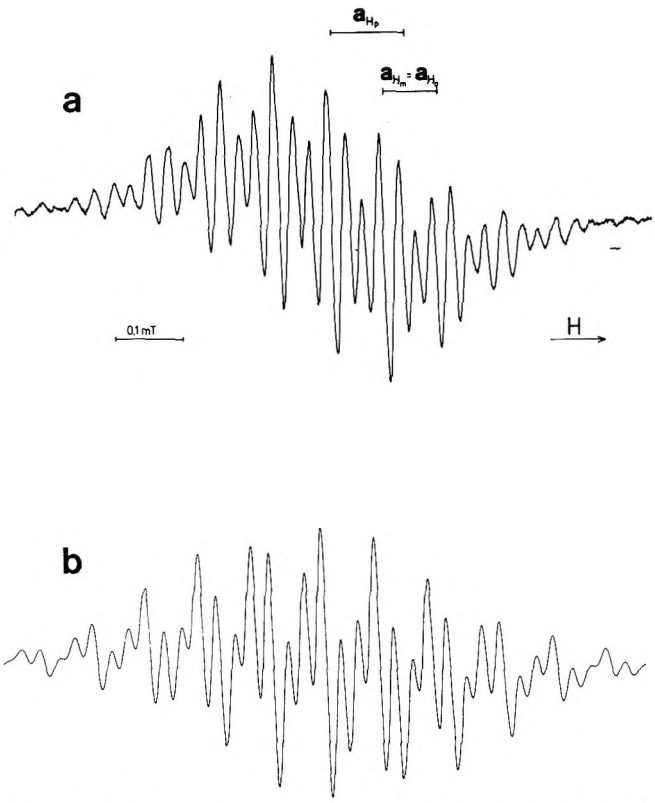


Figure 3. (a) ESR spectrum of 2^- in dimethoxyethane at 270 K. (b) Computer simulation.

produced by simulation only assuming coupling constants for the phenyl protons, e.g., the following set: $a_H^{para} = 0.132$ mT $= 3a_H^{ortho} = 3a_H^{meta} = 3(0.044)$ mT (see Figure 2b). In addition to the 21 lines, at the low- and high-field end of the spectrum a doublet of low intensity appears, which is assigned by its intensity to ^{13}C coupling of the four equivalent carbon atoms of the thieno[3,4-*c*]thiophene fragment. The hyperfine coupling constant amounts to $a_{13C} = 1.146$ mT.

In contrast to the ESR spectrum of the radical cation 2^+, that of the radical anion 2^- is strongly temperature dependent. Whereas below 250 K a spectrum has been recorded (Figure 5) which we were unable to simulate; the spectrum recorded at higher temperature (Figure 3a) can be assigned. It shows a quintet due to the four *p*-phenyl protons which couple with 16 equivalent protons ($a_H^{ortho} \sim a_H^{meta}$). The *g* factor (2.0056, Table I) obtained for 2^- is higher than the one of a free electron ($g_e = 2.0023$)[19] or for the radical cation 2^+ (2.0020, Table I), indicating considerable spin density at the sulfur centers (cf. discussion of Figure 9).

The ESR spectrum of 4^- is shown in Figure 4a. Its interpretation is straight forward: it consists of three triplets due to the coupling of the ring protons with $a_H = 0.490$, 0.435, and 0.184 mT.

Table II. Observed and Calculated Electronic Absorption Spectrum of 2

obsd				calcd (PPP–CI)			
band	$\tilde{\nu}$, cm^{-1}	polarization	log ϵ_{max}	$\tilde{\nu}$, cm^{-1}	symmetry	predominant configuration (%)	f
A	18 180	x	4.07	17 985	x	$\pi_1^* \leftarrow \pi_1$ (99.3)	1.51
				22 717	y	$\pi_2^* \leftarrow \pi_1$ (96.4)	0.00
				27 278	y	$\pi_1^* \leftarrow \pi_2$ (96.6)	0.00
B	26 320	(z)	3.24	28 032	z	$\pi_3^* \leftarrow \pi_1$ (94.3)	0.21
C	29 400		3.77	30 194	z	$\pi_7^* \leftarrow \pi_1$ (92.2)	0.08
				30 264		$\pi_4^* \leftarrow \pi_1$ (98.8)	0.00
				30 268	x	$\pi_6^* \leftarrow \pi_1$ (98.8)	0.00
				30 323	y	$\pi_5^* \leftarrow \pi_1$ (99.0	0.06
D	34 015	z	4.44	35 268	z	$\pi_1^* \leftarrow \pi_3$ (98.8)	0.21
				37 906	z	$\pi_1^* \leftarrow \pi_4$ (94.1)	0.08
E	39 060	x	4.50	39 271	x	$\pi_2^* \leftarrow \pi_2$ (95.3)	1.56

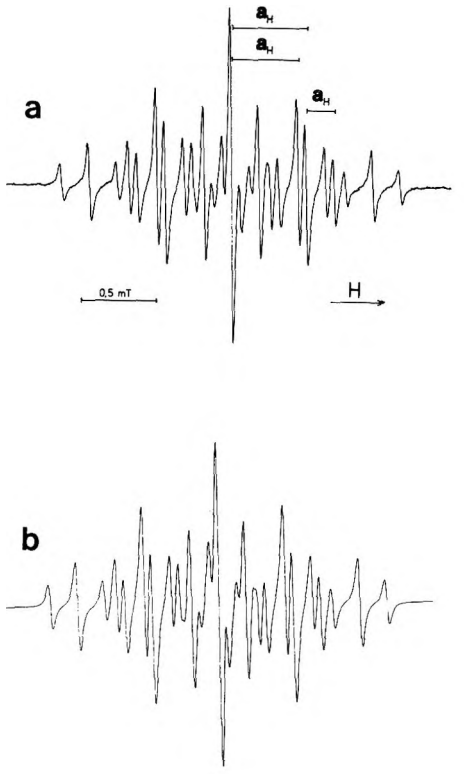


Figure 4. (a) ESR spectrum of 4^- in dimethoxyethane at 220 K. (b) Computer simulation.

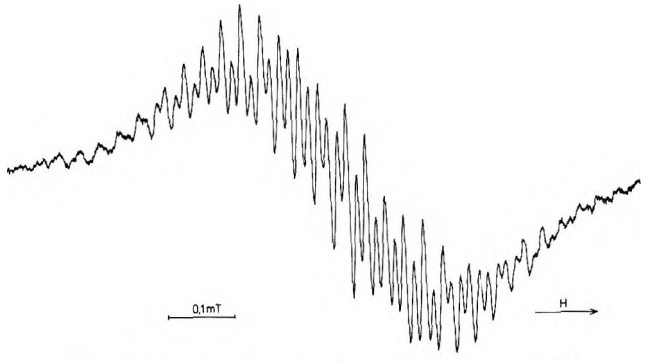


Figure 5. ESR spectrum of 2^- in dimethoxyethane at 210 K.

III. Electronic Absorption Spectrum of 2

The electronic absorption spectrum of **2** in CH_2Cl_2 is shown in Figure 6a. It exhibits five bands in the region between 18 $\times 10^3$ and 40 $\times 10^3$ cm^{-1}. The absorption spectrum of **2** has also been recorded in stretched polyethylene sheets and the

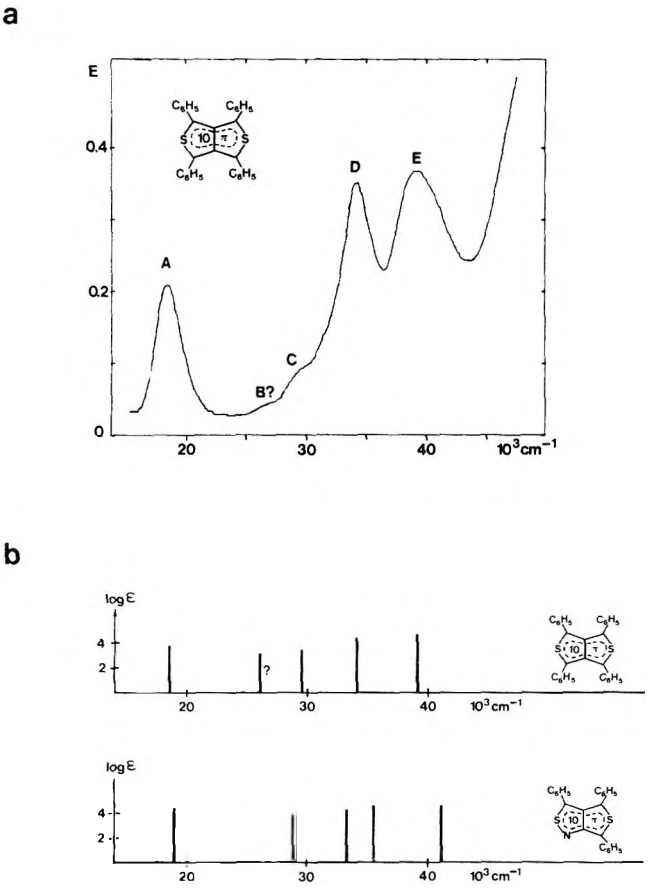


Figure 6. (a) Electronic absorption spectrum of **2** in cyclohexane. (b) Comparison between the first bands of the electronic absorption spectra of **2** and **3**.

polarization direction of bands A, D, and E could be obtained (Table II). An assignment of the observed transitions A–E to the calculated (PPP–CI)[20] ones is indicated in Table II. The calculation predicts several additional weak transitions, which are not observed. They are probably hidden below the intense bands.

According to these calculations the first five bands can be described as due to $\pi \rightarrow \pi^*$ electron transitions. Although the interaction between the pentalene system and the phenyl rings is considerable (see Figure 7), we interpret the first three excited states (bands A, B, and C) as due to one-electron transitions with the transition moment localized mainly within the pentalene moiety.

The lowest electronic absorptions of **2** and **3** are compared in Figure 6b. All bands in the spectrum of **3** are shifted toward higher energy as anticipated from simple perturbation theory.

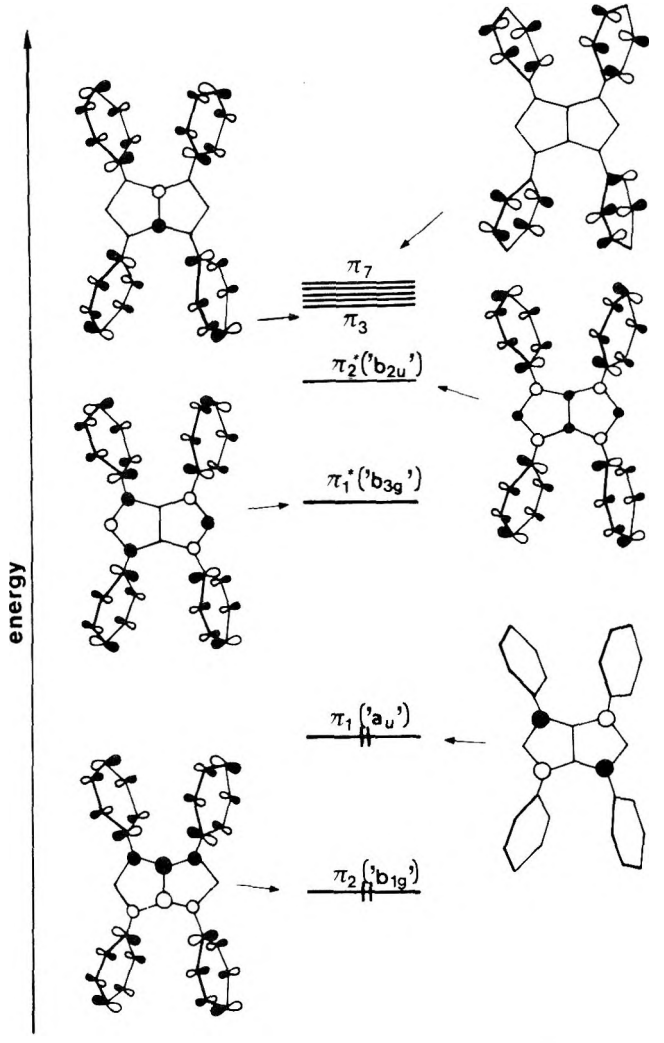


Figure 7. Highest occupied and lowest unoccupied π-MO's of 1 according to a PPP calculation.

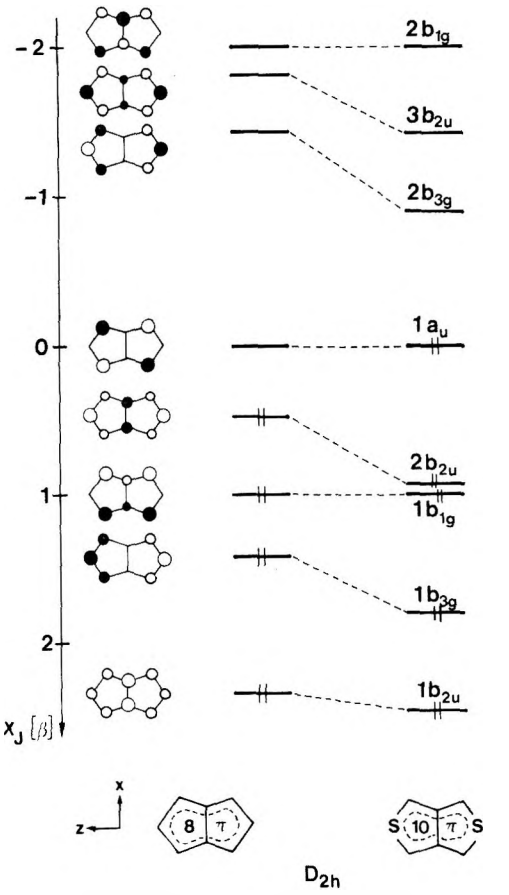


Figure 8. Correlation diagram between the π-MO schemes of pentalene and thieno[3,4-c]thiophene derived from an EH calculation.

The energy difference between the first bands of both absorption spectra, however, is small compared to the difference of the lowest ionizations in both PE spectra. This indicates that in the first ionic state the phenyl participation is less than in the first excited state of **2**.

IV. Discussion

Advantageously, we start by considering the π-MO correlation diagram (Figure 8). At its left are shown the π-MO's of pentalene (**5**) according to an HMO calculation assuming equal bond length. The π-MO's of 1 at the right side were derived from those of **5** by introducing an inductive perturbation at positions 2 and 5, assuming the same resonance integrals as in **5**. The energy levels which are antisymmetric with respect to a vertical plane of symmetry through centers 2 and 5 (b_{1g}, a_u) will remain constant, while the levels which are symmetrical to this plane (b_{2u}, b_{3g}) are lowered due to the higher valence state ionization potential of the sulfur 3p electrons compared with that of the carbon 2p electrons.[22] This perturbation does not affect the LUMO of **5** (a_u), while the next higher orbital, b_{3g}, is lowered considerably.

The MO correlation diagram (Figure 8) implies three corollaries: (i) for the radical cation 1^+ and the radical anion 5^- similar ESR spectra are expected; (ii) analogous to **5**[23] a long wavelength excitation is predicted for **1** due to the small HOMO–LUMO gap; and (iii) the difference between first and second ionization potentials of **1** should be large.

Since both parent compounds, **1** and **5**, are unknown, the first deduction can be verified only in part. The ESR spectrum

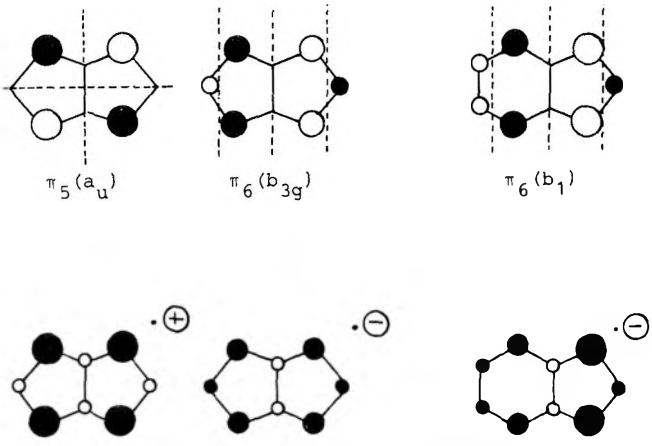
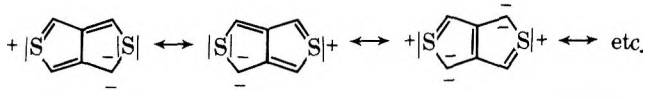


Figure 9. Comparison between the HOMO and LUMO of **2** and LUMO of **4** derived from a HMO calculation ($h_s = 1.2, k_{CS} = 0.7$) (top) and the calculated positive (●) and negative (○) spin densities according to McLachlan[17] (λ 1.2) (bottom).

of the radical anion of an alkyl derivative of 5^+, 1,3,5-tri-*tert*-butylpentalene ($5a^+$), has been reported recently.[24] Using the McConnell equation[25] $a_i^H = \rho_i^\pi |Q|$, which relates the calculated spin densities, ρ_i^π, to the observed proton hyperfine coupling constant, a_i^H, the calculated spin densities for 5^- were found to be 0.25 for the equivalent positions 1, 3, 4, and 6, assuming a $|Q|$ value of 2.7 mT.[24] The spin population calculated for the same positions in 2^+ amounts to 0.316 (Table I) with negative spin densities at other centers. The calculated spin densities according to McLachlan[17] for 2^+, 2^-, and 4^- as well as the corresponding HOMO of **2** and the LUMO's of **2** and **4** are displayed in Figure 9. Obviously, the agreement between experiment and model is excellent.

As concerns the electronic absorption spectra of **2** and **5a** the expected long wavelength bands are observed at 18 180 and 16 800 cm^{-1}, respectively. Both transitions are polarized perpendicular to the long axis of the pentalene moiety.[23]

The predicted large gap between the first two radical cation states, according to our perturbation treatment, due to the stabilization of the $2b_{2u}$ orbital by replacing the CH centers in position 2 and 5 of **5** by sulfur, is observed in the PE spectrum of the tetraphenyl derivative (Figure 1). To elaborate whether 3d participation plays a role as suggested by the valence bond formulation **1a** ↔ **1b** ↔ **1c**, semiempirical calculations of the EH and CNDO/2 type with and without 3d orbitals have been performed. The results indicate that the influence of 3d participation on a_u should be much stronger than on b_{1g} and b_{2g}. A large 3d participation on the sulfur centers would lead to a reduction of the gap between $^2\tilde{A}_u$ and $^2\tilde{B}_{1g}$. The large gap of 1.7 eV observed between the corresponding radical cation states does not require 3d participation. This statement is further corroborated by the relatively large ^{13}C coupling constant and the small g factor found in the ESR experiments on 2^+. According to this, the appropriate representation of **1** and its derivatives would be as indicated in **2** or by valence formulas with dipolar structures as shown below.



Among the possible reasons for the relative stability of the tetraphenyl derivative **2** compared to the parent compound **1**, two should be emphasized: the acceptor properties and the bulkiness of the phenyl group.[7] The latter property renders a reaction at the positions 1, 3, 4, and 6 of **1** less likely.

Experimental Section

The compounds **2** and **4** were prepared according to the literature.[26,27] The PE spectrum of **2** was recorded on a PS 18 photoelectron spectrometer (Perkin-Elmer, Ltd., Beaconsfield) equipped with a heated probe. The calibration was done with Ar.

To generate 2^+ a sample of **2** is oxidized with $AgBF_4$ at 200 K in methylene chloride. Also $AlCl_3$ can be used as oxidizing agent. The radical anion, 2^-, can be generated in dimethoxyethane by treating **2** with potassium at 270 K; 4^- is generated similarly.

The electronic absorption spectrum of **2** was recorded in cyclohexane at room temperature with a Cary 17. To measure the linear dichroism of **2** a polyethylene sheet was swelled with a chloroform solution of the compound. The solvent was allowed to evaporate and the sheet was then stretched and placed over liquid nitrogen in a quartz Dewar.

The dichroic absorption curves and base lines were measured in the way described by Eggers et al.[28]

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Registry No.—**2**, 23386-93-8; **3**, 61164-97-4; **4**, 270-82-6.

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Palladium-Catalyzed Synthesis of Allylic Tertiary Amines from Vinylic Bromides, Olefins, and Secondary Amines

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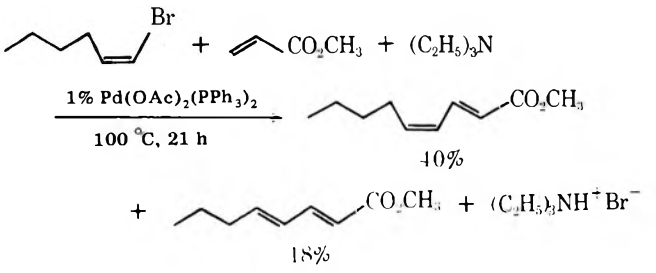
Vinylic bromides, olefins, and basic, unhindered secondary amines react in the presence of a palladium acetate catalyst to form mixtures of dienes and tertiary allylic amines in generally high yields. The reaction is often selective in forming predominantly, or exclusively, one isomeric amine when various vinylic bromides are reacted with 1-hexene and various secondary amines.

The palladium-catalyzed vinylic substitution reaction of α,β-unsaturated esters, styrene, and ethylene with the vinylic group of vinylic halides in the presence of tertiary amines to produce dienes has been reported upon previously.[1] In general, the reactions yielded mixtures of stereoisomers in modest yields. A typical example is the following one.



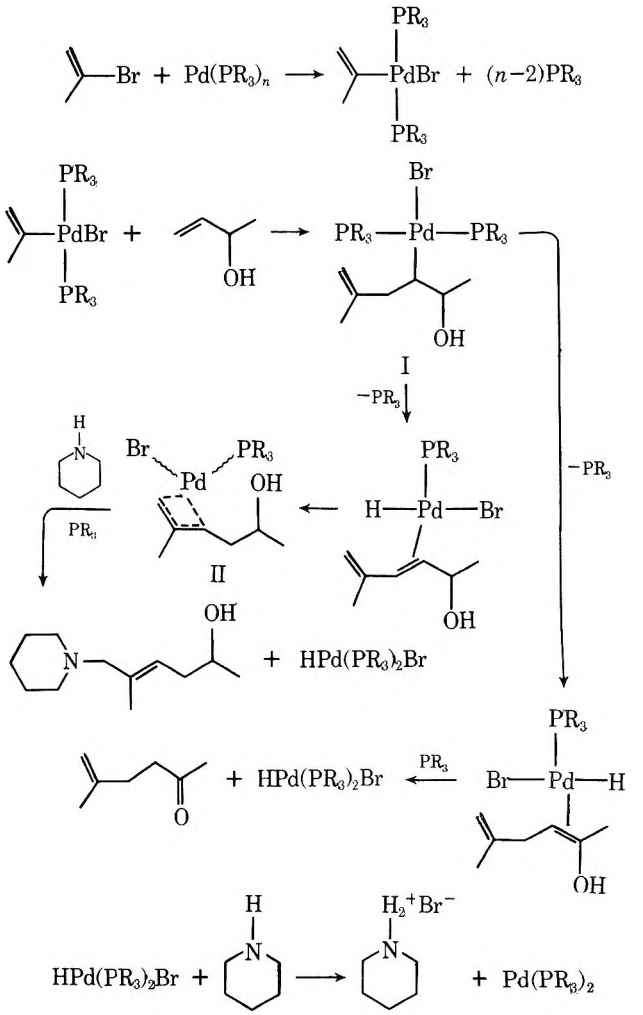
While the selectivity of the reaction can be improved by varying conditions from the 2:1 selectivity above to about 8:1, high stereospecificity was not observed.[1] Since publication of this paper, we have continued to study these reactions. It was clear from our early work that the rates of the reactions and their stereospecificities varied greatly from reactant to reactant. For example, 2-bromopropene reacted both with methyl acrylate[1] and styrene[1] at 100 °C but failed completely to react with 3-buten-2-ol even at higher temperatures.

We proposed previously that the loss of stereochemistry in the vinylic halide reactions was the result of the formation of π-allylic palladium complexes which readily isomerized anti substituents to form the more stable syn structures before they ultimately eliminated the hydridopalladium group to produce the diene.[1] More recently, Larock[2] has shown that presumed vinylic palladium species generated by the exchange reaction of vinylic mercurials with palladium(II) salts do form π-allylic palladium complexes when reacted with olefins. We reasoned that the slow rates and/or incomplete reactions observed in many of our vinylic halide–olefin reactions were due to the formation of relatively stable π-allylic palladium complexes from the catalyst. In order to decompose these complexes under catalytic conditions, we tried employing amines other than the tertiary amines used previously. Certain of these amines have not only turned out to improve the reaction rates dramatically and produce complete reactions but have also altered the products formed.

The amines which are effective in this reaction are unhindered, basic, secondary amines, and the new products produced are allylic tertiary amines. Our preliminary investigation of this reaction is reported herein.

Results and Discussion

The reaction of 2-bromopropene and 3-buten-2-ol with 2% palladium acetate and 4% tri-o-tolylphosphine as catalyst, which did not occur significantly with triethylamine, did take place in 90 min at 100 °C in the presence of 3 equiv of piperidine. The products were 63% of 5-methyl-5-hexen-2-one and 33% of 5-methyl-6-piperidino-4-hexen-2-ol. We presume that the piperidino compound is being formed by a nucleophilic attack of piperidine upon the probable π-allylic palladium intermediate. The reaction of π-crotylpalladium complexes with dimethylamine has been reported to form mainly *N,N*-dimethylcrotylamine.[3]



The initial adduct in the 2-bromopropene–3-buten-2-ol reaction, compound I, apparently eliminates the palladium hydride group in both possible directions. Elimination of hydrogen on the carbon bearing the hydroxyl group yields the π complex of the enol of 5-methyl-5-hexen-2-one, which ultimately dissociates to form the ketone and the palladium hydride. Elimination in the other direction yields a π complex of the conjugated dienol. Since no dienol is observed as a reaction product, this complex must entirely undergo an internal readdition of the hydride to form the π-allylic complex II (or re-form I). Complex II has not yet been isolated, and its detailed structure is not known. Quite possibly the hydroxyl

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group is coordinated with the palladium, thereby stabilizing the complex. The complex, however, does react with piperidine, presumably in an S_N2 fashion, exclusively at the terminal allylic carbon to form the piperidinohexenol. We do not know the stereochemistry of the double bond in the product, but it appears to be a single isomer by GLC and NMR. Presumably, it is the *E* isomer based upon the fact that the π-allylic palladium complexes prefer syn arrangements of substituents on the terminal π-allylic positions.

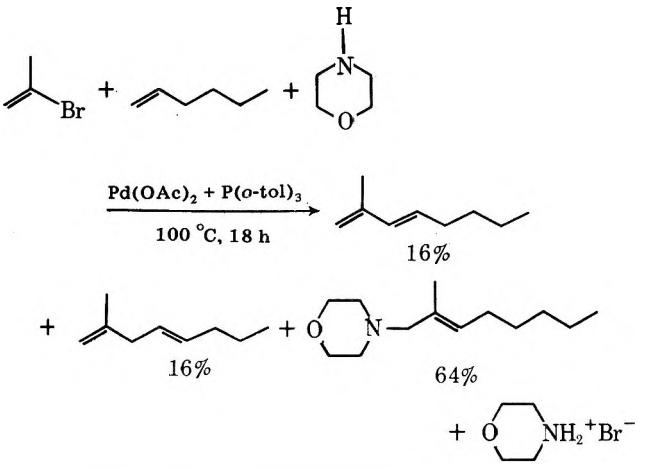
To answer the question, "how general and how selective is the reaction?", we undertook an investigation of the reactions of a series of differently substituted vinylic bromides with 1-hexene and various amines. The results of these reactions are shown in Table I.

The physical properties of the products prepared, NMR spectra, boiling points, and molecular weights, are given in Table II, which appears in the supplementary material.

Vinyl bromide reacts with piperidine in the presence of palladium acetate at 100 °C. We have not determined the products formed (probably acetylene or butadiene), but this reaction occurs more rapidly than the palladium-catalyzed reaction of vinyl bromide with 1-hexene. The competition is more favorable for the olefin reaction when morpholine is used as the base instead of piperidine. Even in this reaction, however, under the usual conditions, about half of the vinyl bromide is lost in the side reaction. The yield of products based upon the vinyl bromide increases with increasing 1-hexene concentration. With a 1-hexene to vinyl bromide ratio of 1.2, the products consist of 3% of *trans*-1,3-octadiene, 3% of 1,4-octadiene, and 47% of *N*-(1-oct-2-enyl)morpholine. The same yields are obtained in the same reaction time in the presence of 2 equiv of tri-*o*-tolylphosphine/equiv of palladium acetate. With a 1-hexene to vinyl bromide ratio of 2.4, the yields increase to 3:3:63, respectively, and with a ratio of 3.6 to 4:4:84, respectively. A small amount of an apparent isomer of the major morpholine adduct is also present in these reaction mixtures. It is probably *N*-(3-oct-1-enyl)morpholine, but we could not isolate a pure sample for identification. Triethylamine does not effectively promote the 1-hexene–vinyl bromide reaction. In 96 h, only 23% of the three octadiene isomers was formed and the vinyl bromide had all reacted. It is notable that in contrast to bromobenzene, where about 20% addition to the second carbon occurred,[4] vinyl bromide adds exclusively to the terminal carbon of the 1-hexene. We also note that the ratios of products in this and the experiments described below do not change with time, showing that the amine products are being formed directly and not by an amination of initially formed dienes.

2-Bromopropene behaves somewhat differently in the reaction with 1-hexene and morpholine. In the absence of an arylphosphine, the bromide is stable in the reaction mixture, but the reaction only consumes about 18% of the bromide and stops. Presumably, an unreactive π-allylic palladium bromide dimer complex is formed, but we have not attempted to identify it yet. The reaction does go to completion if tri-*o*-tolylphosphine is present, in which case 16% of 2-methyl-1,3-octadiene, 16% of 2-methyl-1,4-octadiene, and 64% of *N*-(2-methyloct-2-en-1-yl)morpholine are formed.

In contrast to morpholine, piperidine does cause the complete reaction of 2-bromopropene and 1-hexene even in the absence of an arylphosphine. The reaction products are 93% of *N*-(2-methyloct-2-en-1-yl)piperidine and about 3% each of the 2-methyl-1,3- and 2-methyl-1,4-octadienes. If tri-*o*-tolylphosphine is added, the yield of the piperidine adduct drops to 66% and the dienes increase to 16% each. Tris(2,5-diisopropylphenyl)phosphine in the reaction surprisingly causes less diene formation. In this reaction about 10% of each diene was produced and 74% of the piperidine adduct. The use of triethylamine with the tri-*o*-tolylphosphine catalyst produces an incomplete reaction forming equal amounts, 14% each, of three dienes: the 2-methyl-1,3- and 2-methyl-1,4-octadienes found in the other reactions and, in addition, 2-methyl-2,4-octadiene. In all of the reactions of 2-bromopropene, addition of the 2-propenyl group occurred only to the terminal carbon of the 1-hexene.



Both *trans*- and *cis*-1-bromo-1-propene react with 1-hexene and morpholine in the absence of a phosphine. In the presence or absence of tri-*o*-tolylphosphine, both bromides produce three dienes and two morpholine adducts. Products arise from addition of the 1-propenyl group in both directions to the 1-hexene. The trans bromide in the presence of the phosphine yields 18% of (*E*,*E*)-2,4-nonadiene, 18% of (*E*)-2-butyl-1,3-pentadiene (?), 5% of an unknown diene (probably 2,5-nonadiene), 34% of *N*-(2-non-3-enyl)morpholine, and 11% of *N*-(4-methyloct-3-en-2-yl)morpholine. The ratio of the terminal to internal addition to the 1-hexene is ~1.8. It is interesting that the ratio is considerably higher, ~2.3, in the absence of the phosphine. The cis bromide in the presence of the phosphine produces 15% of (*Z*,*E*)-2,4-nonadiene, 15% of (*E*)-2-butyl-1,3-pentadiene (same isomer as obtained from the trans bromide), 6% of the unknown diene, 42% of *N*-(2-non-3-enyl)morpholine and 15% of *N*-(4-methyloct-3-en-2-yl)morpholine. The ratio of terminal to internal products is 1.8, the same as observed with the trans bromide. In the absence of the phosphine, the cis isomer shows a terminal to internal isomer ratio of ~2.1. The presence of the tri-*o*-tolylphosphine in both the cis and trans reactions increases the amount of dienes formed by 11–16% and decreases the amount of morpholine addition products by a corresponding amount. The use of the tris(2,5-diisopropylphenyl)phosphine in the *cis*-1-bromo-1-propene reaction seems to have little influence on the reaction since the results are similar to those obtained in the absence of a phosphine.

cis-1-Bromo-1-hexene was reacted with morpholine and ethylene in order to compare the products formed with those from vinyl bromide, morpholine, and 1-hexene. The reaction products were 5% of *cis*-1,3-octadiene, 84% of *N*-(2-oct-3-enyl)morpholine, and 11% of *N*-(4-oct-2-enyl)morpholine. Essentially, the same ratio of products is obtained at one-tenth the rate using diethylamine in place of morpholine. As expected by the π-allylic mechanism, the morpholine adducts obtained from the bromohexene reaction are different from those obtained in the vinyl bromide reaction.

The products formed in the reaction of 2-methyl-1-bromo-1-propene with morpholine and 1-hexene clearly show that electronic factors are significant in determining the direction of addition of the vinylic groups to 1-hexene since terminal to internal addition ratios were lower than in the 1-bromo-1-propene reactions. In the absence of a triarylphosphine, this reaction reaches completion in 96 h, forming a mixture of six dienes and two morpholine adducts. The two

Table I. Palladium-Catalyzed Reactions of Vinylic Bromides with 1-Hexene and Amines[a]

vinylic bromide	amine[b]	PAr_3	reaction time, h at 100 °C	products, (% yield) dienes[c]	products, (% yield) amines[c]	% terminal/ % internal
vinyl bromide	M		21	(*E*)-1,3-octadiene (3)[d] (*E*)-1,4-octadiene (3)[d]	1-(*N*-morpholino)-2-octene (47)[d] unknown (5)[d]	>20[e]
vinyl bromide	M	P(o-tol)$_3$	18	(*E*)-1,3-octadiene (5) (*E*)-1,4-octadiene (5)	1-(*N*-morpholino)-2-octene (48) unknown (1)	>20[e]
vinyl bromide[f]	M	P(o-tol)$_3$	21	(*E*)-1,3-octadiene (3)[d] (*E*)-1,4-octadiene (3)[d]	1-(*N*-morpholino)-2-octene (63)[d] unknown (5)[d]	>20[e]
vinyl bromide[g]	M	P(o-tol)$_3$	16	(*E*)-1,3-octadiene (4)[d] (*E*)-1,4-octadiene (4)[d]	1-(*N*-morpholino)-2-octene (84)[d] unknown (2)[d]	>20[e]
vinyl bromide	T	P(o-tol)$_3$	96	(*E*)-1,3-octadiene (5)[d] (*E*)-1,4-octadiene (5)[d] (*E,E*)-2,4-octadiene (13)[d]		>20[e]
2-bromopropene	M		60[h]	(*E*)-2-methyl-1,3-octadiene (3)[d] (*E*)-2-methyl-1,4-octadiene (3)[d]	1-(*N*-morpholino)-2-methyl-2-octene (12)[d]	>20
2-bromopropene	M	P(o-tol)$_3$	68	(*E*)-2-methyl-1,3-octadiene (16) (*E*)-2-methyl-1,4-octadiene (16)	1-(*N*-morpholino)-2-methyl-2-octene (64)	>20
2-bromopropene	P		48	(*E*)-2-methyl-1,3-octadiene (3)[d] (*E*)-2-methyl-1,4-octadiene (3)[d]	1-(*N*-piperidino)-2-methyl-2-octene (93)[d]	>20
2-bromopropene	P	P(o-tol)$_3$	68	(*E*)-2-methyl-1,3-octadiene (16) (*E*)-2-methyl-1,4-octadiene (16)	1-(*N*-piperidino)-2-methyl-2-octene (66)	>20
2-bromopropene	P	P(2,5-*i*-Pr_2Ph)$_3$	56	(*E*)-2-methyl-1,3-octadiene (10)[d] (E)-2-methyl-1,4-octadiene (10)[d]	1-(*N*-piperidino)-2-methyl-2-octene (66)	>20
2-bromopropene	T	P(o-tol)$_3$	60[h]	(*E*)-2-methyl-1,3-octadiene (14) (*E*)-2-methyl-1,4-octadiene (14) (*E*)-2-methyl-2,4-octadiene (14)		>20
(*E*)-1-bromo-1-propene	M		32	(*E,E*)-2,4-nonadiene (10)[d] (*E*)-2-*n*-butyl-1,3-pentadiene (10)[d] unknown (5)[d]	*N*-(2-non-3-enyl)morpholine (51)[d] *N*-(4-methyloct-3-en-2-yl)-morpholine (17)[d]	~2.3
(*E*)-1-bromo-1-propene	M	P(o-tol)$_3$	47	(*E,E*)-2,4-nonadiene (18) (*E*)-2-*n*-butyl-1,3-pentadiene (18) unknown (5)	*N*-(2-non-3-enyl)morpholine (34) *N*-(4-methyloct-3-en-2-yl)-morpholine (11)	~1.8
(*Z*)-1-bromo-1-propene	M		30	(*Z,E*)-2,4-nonadiene (10)[d] (*E*)-2-*n*-butyl-1,3-pentadiene (10)[d] unknown (5)[d]	*N*-(2-oct-3-enyl)morpholine (52)[d] *N*-(4-methyloct-3-en-2-yl)-morpholine (20)[d]	~2.1
(*Z*)-1-bromo-1-propene	M	P(o-tol)$_3$	40	(*Z,E*)-2,4-nonadiene (15) (*E*)-2-*n*-butyl-1,3-pentadiene (15) unknown (6)	*N*-(2-oct-3-enyl)morpholine (42) *N*-(4-methyloct-3-en-2-yl)-morpholine (15)	1.8[e]
(*Z*)-1-bromo-1-propene	M	P(2,5-*i*-Pr_2Ph)$_3$	50	(*Z,E*)-2,4-nonadiene (6)[d] (*E*)-2-*n*-butyl-1,3-pentadiene (6)[d] unknown (3)[d]	*N*-(2-oct-3-enyl)morpholine (40)[d] *N*-(4-methyloct-3-en-2-yl)-morpholine (18)[d]	~1.9

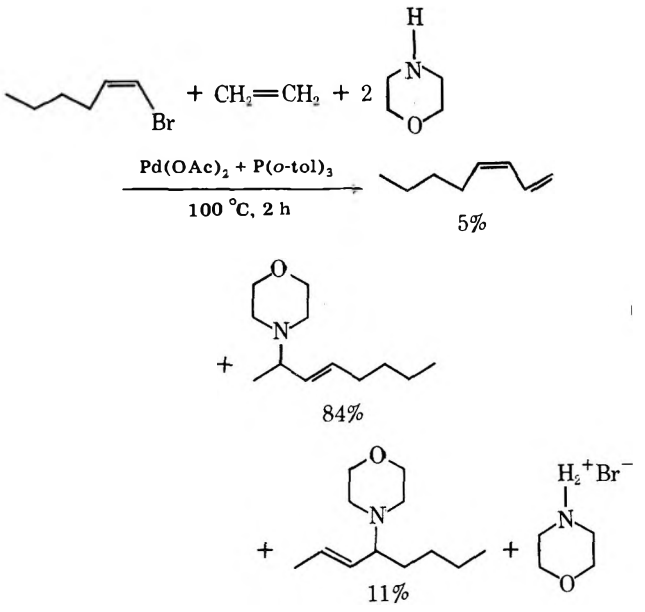
Table I *(Continued)*

vinylic bromide	amine[b]	PAr_3	reaction time, h at 100 °C	products, (% yield) dienes[c]	products, (% yield) amines[c]	% terminal/ % internal
(*Z*)-1-bromo-1-hexene[i]	M	P(*o*-tol)$_3$	2	(*Z*)-1,3-octadiene (5)[d]	*N*-(2-oct-3-enyl)morpholine (84)[d] *N*-(4-oct-2-enyl)morpholine (11)[d]	∞
(*Z*)-1-bromo-1-hexene[i]	D	P(*o*-tol)$_3$	20	(*Z*)-1,3-octadiene (5)[d]	2-diethylamino-3-octene (82)[d] unknown (7)[d]	∞
2-methyl-1-bromo-1-propene	M		96	(*E*)-2-methyl-2,4-nonadiene (25)[d] 2-*n*-butyl-4-methyl-1,3-pentadiene (8)[d] 4 unknowns (31)[d]	*N*-(2-methylnon-3-en-2-yl)morpholine (13) unknown (7)	
2-methyl-1-bromo-1-propene	M	P(*o*-tol)$_3$	48	(*E*)-2-methyl-2,4-nonadiene (13) 2-*n*-butyl-4-methyl-1,3-pentadiene (15) 4 unknowns (30)	*N*-(2-methylnon-3-en-2-yl)morpholine (31)	1.7[e]
2-methyl-1-bromo-1-propene	P		48	(*E*)-2-methyl-2,4-nonadiene (23)[d] 2-*n*-butyl-4-methyl-1,3-pentadiene (5)[d] 4 unknowns (22)[d]	*N*-(2-methylnon-3-en-2-yl)piperidine (21)[d] unknown (3)[d]	
2-methyl-1-bromo-1-propene	P	P(*o*-tol)$_3$	48	(*E*)-2-methyl-2,4-nonadiene (14) 2-*n*-butyl-4-methyl-1,3-pentadiene (11) 4 unknowns (31)	*N*-(2-methylnon-3-en-2-yl)piperidine (35)	1.3
2-methyl-1-bromo-1-propene	DIPA	P(*o*-tol)$_3$	72[j]	(*E*)-2-methyl-2,4-nonadiene (30)[d] 2-*n*-butyl-4-methyl-1,3-pentadiene (30)[d] 4 unknowns (30)[d]		
2-methyl-1-bromo-1-propene	T	PPh_3	96	no reaction		
2-methyl-1-bromo-1-propene	T	P(*o*-tol)$_3$	48[j]	(*E*)-2-methyl-2,4-nonadiene (40) 2-*n*-butyl-4-methyl-1,3-pentadiene (50) 4 unknowns (10)		1.0[e]
2-methyl-1-bromo-1-propene	T	P(2,5-*i*-$Pr_2Ph)_3$	72[g,j]	(*E*)-2-methyl-2,4-nonadiene (32)[d] 2-*n*-butyl-4-methyl-1,3-pentadiene (27)[d] 4 unknowns (25)[d]		
methyl (*E*)-3-bromo-2-methylpropenoate	T	P(*o*-tol)$_3$	20	methyl (*E*,*E*)-2-methyl-2,4-nonadienoate (63) 5 unknowns (25)		4.6[e]

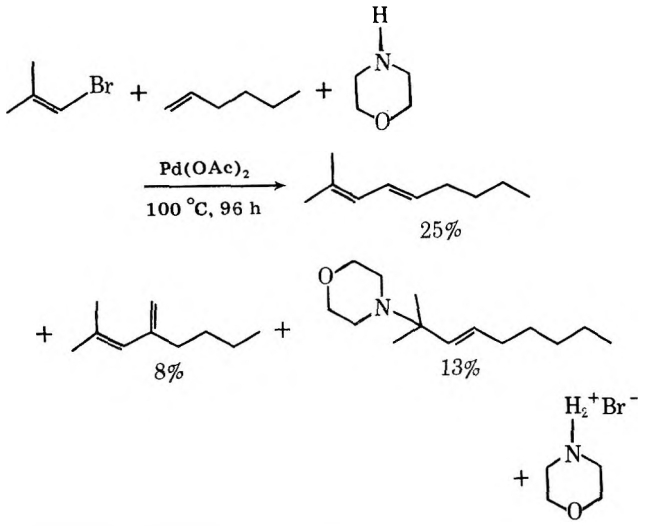
[a] The normal reaction conditions were the following: 10 mmol of vinylic bromide; 12 mmol of 1-hexene; 30 mmol of amine; 0.10 mmol of palladium acetate; and 0.20 mmol of triarylphosphine, if used. The mixtures became homogeneous on warming and were heated in capped Pyrex tubes at 100 °C until the vinylic bromide disappeared as determined by GLC or the reaction stopped. [b] M = morpholine, P = piperidine, D = diethylamine, T = triethylamine, and DIPA = diisopropylamine. [c] Relative amounts of isomers present in mixtures were estimated by GLC assuming equal sensitivity to the GLC detector. [d] Yields were determined by GLC using internal standards calibrated with known samples isolated by preparative GLC. [e] Calculated using the ratio of isomeric dienes determined by complete hydrogenation of the diene mixture. [f] Used 24 mmol of 1-hexene instead of 12. [g] Used 36 mmol of 1-hexene instead of 12. [h] Reaction stopped before vinylic bromide had all reacted. [i] Reacted with ethylene under 200 psi using 4 mL of acetonitrile as solvent. [j] Twice the normal amounts of palladium acetate and triarylphosphine were used.

major dienes are 2-methyl-2,4-nonadiene (25%) and 2-butyl-4-methyl-1,3-pentadiene (8%). Unexpectedly, the major morpholine adduct obtained is the allylic tertiary amine *N*-(2-methylnon-3-en-2-yl)morpholine (13%). The minor morpholine adduct (7%) was not identified.

This reaction proceeded more rapidly in the presence of tri-*o*-tolylphosphine (48 h) and produced only one morpholine adduct, *N*-(2-methylnon-3-en-2-yl)morpholine, in 31% yield. The formation of the related unexpected tertiary allylic amine occurred when piperidine was used in place of morpholine. The structure of these unexpected amines was established from several pieces of evidence. The NMR spectra alone are quite conclusive based upon the presence of two vinylic protons rather than the one in the allylic isomer and by the chemical shift of the gem dimethyl on the carbon bearing the amine function at δ 1.10. If the methyls were on a double-bond carbon, they would appear at δ 1.60 (in 2-methyl-2-butene, for example). Hydrogenation of the morpholine adduct in acetic



acid with platinum oxide as catalyst at 15 psig gave 2-methylnonane as the sole product. The highly hindered nature of the amine is shown by the fact that it fails to react with methyl



iodide over a period of several days at room temperature. The mass spectra of both the morpholine and piperidine adducts show major peaks at M − 15 with only a very weak parent peak in the piperidine case and none in the morpholine adduct. Loss of one of the methyls in the gem dimethyl group would be expected since a highly stabilized carbonium ion would be formed. In contrast to these compounds, the other amine adducts prepared in this study all show significant parent ion peaks. We do not have an explanation for the formation of the more hindered amines in these reactions, but we are now looking at the behavior of isolated π-allylic palladium complexes with secondary amines with the hope of finding an explanation. Probably differences in the trans and cis ligands or in the π- or σ-allylic structures are responsible for the unusual products.

The 2-methyl-1-bromo-1-propene–1-hexene reaction goes to completion, even with the hindered diisopropylamine or triethylamine. With diisopropylamine and tri-*o*-tolylphosphine, the reaction gives a mixture of dienes: 30% of 2-methyl-2,4-nonadiene, 30% of 2-butyl-4-methyl-1,3-pentadiene, and 30% of four other unidentified (presumed) ten-carbon dienes. With triethylamine, the composition of the diene mixture was shown to be dependent upon the arylphosphine employed. Triphenylphosphine caused only a few percent reaction in 48 h, while tri-*o*-tolylphosphine produced a complete reaction in the same time. The products were 40% of 2-methyl-2,4-nonadiene, 50% of 2-butyl-4-methyl-1,3-pentadiene, and 10% of four other dienes. The use of tris(2,5-diisopropylphenyl)phosphine changed the product yields to 32, 27, and 25%, respectively. The yields of the various dienes in these reactions therefore may vary significantly with the reactants and reaction conditions.

Further evidence of the importance of electronic effects in determining the direction of addition of vinylic halides to alkenes was found in the reaction of methyl (*E*)-3-bromo-2-methylacrylate with 1-hexene. Unhindered secondary amines cannot be used in this reaction because Michael additions and amide formation occur under the reaction conditions. With triethylamine, the reaction goes well, however, presumably because the carboxyl group facilitates elimination and dissociation of the palladium hydride group. The major product, 63%, of this reaction is (presumed *E*) methyl 2-methyl-2,4-nonadienoate. Five other minor products which have similar GLC retention times, obtained in 25% yield, are believed to be other isomers of this ester. Complete hydrogenation of the mixture reveals that two basic carbon skeletons are present, that formed by terminal addition of the bromo ester and that formed by addition of it to the second carbon of the 1-hexene. The ratio of the two was 4.6, considerably less than the 1.0 value obtained in the addition of 1-bromo-2-methyl-1-propene to 1-hexene under similar conditions. The change is in the direction expected if the ester group withdraws electrons from the terminal vinyl carbon relative to methyl, and therefore this causes the vinyl group to add more easily to the more negative terminal carbon of the 1-hexene. Previously we observed essentially complete terminal addition of this bromide to methyl acrylate.[1] The direction of addition depends upon the substituents in both reactants.

Several trends can be seen in the data in Table I which will be of value in predicting the products which will be formed in various vinylic halide–olefin reactions.

(1) Vinyl bromide and α-substituted vinylic bromides add exclusively to the less substituted carbon of a double bond.

(2) β-Substituted vinylic halides may add either way to an unsymmetrical double bond. The less substituted carbon is preferred and may be the only position attacked if the β substituent or substituents are electron withdrawing. Selective attack at the double-bond carbon β to an electron-withdrawing group in the olefin will occur if there are no major steric problems at this site.

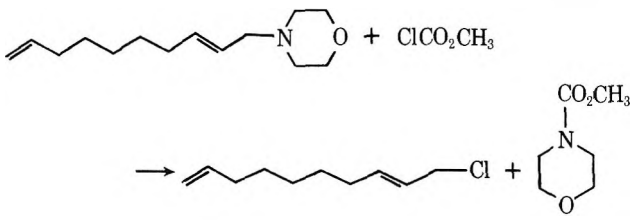
(3) Dienes formed in the reaction of olefins with vinylic bromides and basic unhindered secondary amines generally retain the stereochemistry present in the vinylic bromide double bond to a high degree. The amine adducts lose any stereochemistry present in the vinylic bromides. If triethylamine is used as the base, stereochemistry in the dienes may be lost and double-bond migration may occur.

(4) Amine attack upon the presumed π-allylic palladium complex intermediate occurs at the least substituted or least hindered end of the allylic systems unless a tertiary–secondary system is present, in which case tertiary attack may occur.

(5) Many vinylic bromide–olefin–secondary amine reactions occur in the absence of triarlyphosphines, but all do not. Tri-*o*-tolylphosphine is often useful to cause slow or incomplete reactions to go faster and in higher yield. Product ratios may also be altered by use of a phosphine with the palladium acetate catalyst.

From the results reported in Table I, it is clear that the palladium-catalyzed vinylic substitution reaction will have some important applications in aliphatic chemistry as well as in the aromatic areas reported upon previously. Since allylic tertiary amines are readily converted into other types of compounds by reactions such as the von Braun, Hofmann elimination, hydrogenolysis, and Polonovski reactions, the

vinylic substitution will be generally useful. For example, we have converted 1-(*N*-morpholino)-2,9-decadiene (obtained from vinyl bromide, 1,7-octadiene, and morpholine in 80% yield) into 1-chloro-2,9-decadiene in 69% (isolated) yield by



a very useful modification of the von Braun reaction with methyl chloroformate.[5] The reaction occurred in 4 h at room temperature, and none of the 3-chloro allylic isomer was seen.[6]

The tolerance of the olefinic substitution reactions for nearly all functional groups[7,8] may make this method of major synthetic value in the preparation of complex polyfunctional aliphatic structures.

Experimental Section

Reagents. The amines used were all commercial materials used without further purification, but they were dried and stored over Linde 4A molecular sieves. Palladium acetate,[9] tri-*o*-tolylphosphine,[6] tris(2,5-diisopropylphenyl)phosphine,[5] *cis*-1-bromo-1-hexene,[10] and 1-bromo-2-methyl-1-propene[11] were prepared by published procedures. The methyl (*E*)-3-bromo-2-methylpropenoate was obtained by the method of Canbere,[13] but heating of the reaction mixture was necesary to get mainly the *E* isomer (95%). Vinyl bromide (Aldrich), 2-bromopropene (Chemical Samples Co.), and 1-bromo-1-propene (Columbia Organic Chemicals) were commercial samples, but the 1-bromo-1-propene was fractionated to separate 95% pure samples of the cis and trans isomers.

The Reaction of 2-Bromopropene with 3-Buten-2-ol and Piperidine. A solution of 0.449 g (2.0 mmol) of palladium acetate and 1.216 g (4.0 mmol) of tri-*o*-tolylphosphine in 12.1 g (100 mmol) of 2-bromopropene, 30 mL (~300 mmol) of piperidine, and 8.0 g (110 mmol) of 3-buten-2-ol was heated at 100 °C in a steam bath in a capped 200 mL Pyrex bottle for 90 min. Analysis at 125 °C on a 10 ft 20% DC-550 column showed that all of the bromide had reacted. The cooled, semisolid reaction mixture was rinsed into a separatory funnel with ether and water. The ether layer was separated, washed twice with 100-mL portions of water, dried over potassium carbonate and distilled. There was obtained 7.0 g (63%) of 5-methyl-5-hexen-2-one, bp 100 °C (185 mm), and 6.5 g (33%) of 5-methyl-6-piperidino-4-hexen-2-ol, bp 142 °C (15 mm).

General Procedure for the Reaction of Vinylic Bromides with Hexene and Amines. A solution of 0.0224 g (0.1 mmol) of palladium acetate and 0.061 g (0.2 mmol) of tri-o-tolylphosphine, or an equivalent amount of another phosphine if one is used, in 10 mmol of the vinylic bromide, 30 mmol of the secondary amine or triethylamine, and 1.00 g (12 mmol) of 1-hexene was heated in a capped heavy-walled "Pyrex" tube at 100 °C until GLC analysis of the solution showed that the bromide had all reacted or else that the reaction had ceased. Samples for VPC analysis were removed from the hot reaction mixture by syringe through a needle injected through a small hole in the metal cap and the self-sealing rubber cap liner. Analyses of the cooled reaction mixtures were generally performed by GLC on a 10 ft × 0.25 in 20% DC-550 column by adding an internal standard either before the reaction or afterwards using predetermined sensitivity coefficients for the products to calculate yields. Generally, naphthalene, alkylnaphthalenes, or alkylbenzenes were used as the internal standards. For preparative scale experiments, the reactions were carried out with ten times the amounts given and the products were isolated as described in the preceding experiment.

Hydrogenation of Diene Mixtures. A solution of 10 mmol of the diene mixture dissolved in 10 mL of acetic acid and 100 mg of 5% platinum on carbon (Engelhard Industries) in a 60 mL Parr bomb was hydrogenated at room temperature with magnetic stirring under 500 psi of hydrogen until absorption stopped. The pressure was released, the catalyst was removed by filtration, and the filtrate was diluted with water. The product was extracted with ether, and after washing the ether with aqueous base the solution was dried and concentrated. Products were than purified by preparative GLC.

Acknowledgment. We are grateful to the National Science Foundation for providing financial support for this work and to the Matthey-Bishop Co., Inc., for the loan of the palladium used as catalyst.

Registry No.—Vinyl bromide, 593-60-2; 2-bromopropene, 557-93-7; (*E*)-1-bromo-1-propene, 590-15-8; (*Z*)-1-bromo-1-propene, 590-13-6; (*Z*)-1-bromo-1-hexane, 13154-12-6; 2-methyl-1-bromo-1-propene, 3017-69-4; methyl (*E*)-3-bromo-2-methylpropenoate, 40053-01-8; morpholine, 110-91-8; triethylamine, 121-44-8; piperidine, 110-89-4; tri-o-tolylphosphine, 109-89-7; diisopropylamine, 108-18-9; (*E*)-1,3-octadiene, 39491-65-1; (*E*)-1,4-octadiene, 53793-31-0; (*E,E*)-2,4-octadiene, 60919-80-4; (*E*)-2-methyl-1,3-octadiene, 67350-81-6; (*E*)-2-methyl-1,4-octadiene, 67350-82-7; (*E,E*)-2,4-nonadiene, 56700-78-8; (*E*)-2-*n*-butyl-1,3-pentadiene, 67350-83-8; (*Z,E*)-2,4-nonadiene, 67350-84-9; (*Z*)-1,3-octadiene, 39491-64-0; (*E*)-2-methyl-2,4-nonadiene, 67350-85-0; 2-*n*-butyl-4-methyl-1,3-pentadiene, 67350-86-1; methyl (*E,E*)-2-methyl-2,4-nonadienoate, 61382-50-1; 1-(*N*-morpholino)-2-octene, 67350-87-2; 1-(*N*-morpholino)-2-methyl-2-octene, 67350-88-3; 1-(*N*-piperidino)-2-methyl-2-octene, 67350-89-4; *N*-(2-non-3-enyl)morpholine, 67350-90-7; *N*-(4-methyloct-3-en-2-yl)morpholine, 67350-91-8; *N*-(2-oct-3-enyl)morpholine, 67350-92-9; *N*-(4-oct-2-enyl)morpholine, 67350-93-0; 2-(diethylamino)-3-octene, 67350-94-1; *N*-(2-methylnon-3-en-2-yl)morpholine, 67350-95-2; *N*-(2-methylnon-3-en-2-yl)piperidine, 67350-96-3; 1-hexene, 592-41-6; 5-methyl-5-hexen-2-one, 3240-09-3; 5-methyl-6-piperidino-4-hexen-2-ol, 67350-97-4; 2-methylnonane, 871-83-0; 2,4-dimethyloctane, 4032-94-4; methyl 2-methylnonanoate, 56898-37-4; methyl 2,4-dimethyloctanoate, 67350-98-5.

Supplementary Material Available: Table II, containing NMR spectra, boiling points, and molecular weights of the products prepared (7 pages). Ordering information is given on any current masthead page.

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Synthesis and Structure Proof of C-2 and C-4 Monofunctional Brexanes and Brendanes

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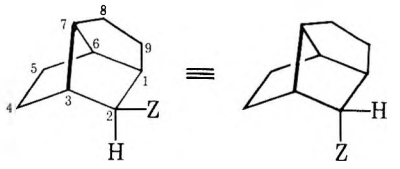
The C_9 skeletons in tricyclo[4.3.0.$0^{3,7}$]nonane ("brexane") and tricyclo[4.2.1.$0^{3,7}$]nonane ("brendane") on the one hand and in tetracyclo[4.3.0.$0^{2,4}$.$0^{3,7}$]nonane ("deltacyclane") on the other are perceived as interesting homologocycles of norbornane and nortricyclane, respectively. For example, brexyl derivatives are chiral and are uniquely structured so that a substituent at C-2 is simultaneously exo to one norbornyl unit and endo to another. Therefore, the ease of ionization of the C-2 substituent can, among other things, reveal the relative importance of "anchimeric assistance" and "steric hindrance to departure" because these two "norbornyl" features oppose each other. This paper describes the preparation and characterization of key monofunctionalized brexanes and brendanes. Brexan-2-one (**10**) was synthesized from a 7-carboxynorbornyl precursor (**6a**) through a sequence that involved lengthening the C-7 chain and ring closure by internal alkylation. Deltacyclane (**21**) was obtained from norbornadiene by four different routes and provides convenient access to brexan-4-one (**24**) and brendan-2-one (**25**) through cleavage of the cyclopropyl ring. We prepared brendan-4-one (**31**) from a known norbornenecarboxylic acid (**28a**) by transformations that involved formation and directed opening of tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]nonan-3-one (**29**). The brexyl and brendyl skeletons were confirmed by cleavage to known bicyclo[3.3.0]octyl systems and were interrelated with deltacyclane by carbene insertion reactions. With KO-*t*-Bu/*t*-BuOH at 185 °C brexan-2-one rearranges to brendan-2-one. This conversion illustrates the potential utility of alkali-induced skeletal changes via homoenolate ions.

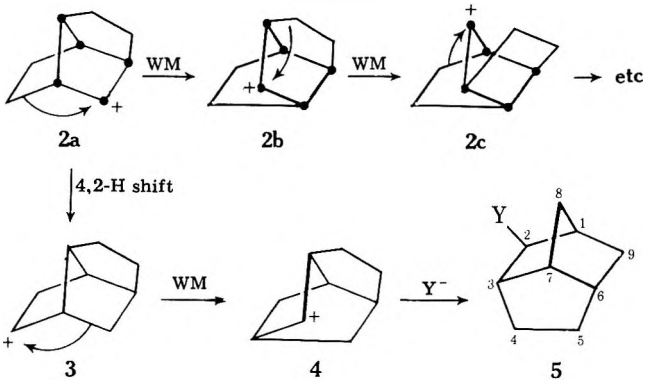
At a time of intense research activity in norbornyl chemistry we pointed out the unique features of the tricyclic C_9 analogue **1**, which we called "brexane", and recommended its study in connection with the "classical–nonclassical" cation controversy.[1] Two norbornyl units can be identified in brexane[2] and these are so arranged that a substituent Z at C-2 is simultaneously exo to one norbornyl unit and endo to the other. Furthermore, interchange of H and Z at C-2 produces neither a diastereomer nor an enantiomer, but a molecule superimposable on the original; i.e., **1a** ≡ **1b**. In norbornyl



1a **1b**

systems, exo derivatives solvolyze faster than do the corresponding endo analogues, but chemists disagree as to whether these differences should be attributed to abnormally high exo rates (due to anchimeric assistance) or to abnormally low endo rates (due to steric interference by an endo hydrogen directly across the ring.[3] The ionization behavior of brex-2-yl systems can uniquely reveal the relative importance of anchimeric assistance and steric interference because both of these factors act on Z simultaneously but oppose each other. Like its norbornyl counterpart, the tricyclic cation **2a** from departure of Z regenerates its mirror image on Wagner–Meerwein rearrangement (e.g., **2a** and **2b** are enantiomers), but has the added novel feature that repetitive rearrangements (e.g., **2a** → **2b** → **2c** → etc., Scheme I) involve consecutive shifts of antiparallel bonds and transfer the positive charge successively to every atom of the core ring, identified in **2a** by heavy dots. In contrast to norbornyl systems, however, 1,2-hydrogen shifts are precluded by the bridgeheads; and 1,3-hydrogen shifts (e.g., from C-4 to C-2 in **2a**) are separately detectable because they produce a new ion (**3**), which can terminate to give brex-4-yl derivatives or which can, by a single Wagner–Meerwein shift (**3** → **4**), give the brendane[4] skeleton **5** (Scheme I). In this paper we describe our syntheses, characterization, and interconversions of monofunctionalized brexanes, brendanes, and related systems. These full details[5] provide

Scheme I



the structural foundation for our own mechanistic work as well as for a variety of studies from other laboratories involving brexyl and brendyl skeletons.[6]

We divide the presentation into these six parts: (I) synthesis of brexan-2-ol; (II) routes to deltacyclane; (III) synthesis of brex-4-yl and brend-2-yl systems; (IV) synthesis and structure proof of brendan-4-one; (V) structural correlations in brexyl and brendyl systems; and (VI) skeletal rearrangements via homoenolate ions. Each part is accompanied by an appropriate formula scheme.

I. Synthesis of Brexan-2-ol. We prepared this C_9 target alcohol as outlined in Scheme II. The known keto acid **6a** was converted to the homologous, keto ester **7** in an overall yield of 43% by an Arndt–Eistert sequence (**6a** → **6b** → **6c** → **7**). The intermediate liquid acid chloride **6b** was not purified, but the crystalline diazomethyl ketone **6c** was fully characterized. Reduction of liquid keto ester **7** with lithium aluminum hydride gave a liquid mixture of epimeric diols (**8**). This diol mixture was selectively monoesterified at the primary alcohol with methanesulfonyl chloride and, without isolation, the monomesylate **8b** was oxidized with Brown's reagent to the liquid keto mesylate **9** and directly cyclized to brexan-2-one (**10**) by the action of NaH in *N*,*N*-dimethylformamide. This liquid ketone incorporated no deuterium in D_2O/K_2CO_3, formed no precipitate with sodium bisulfite, shows a split carbonyl peak in the infrared (1844 w and 1748 s), and gives a crystalline semicarbazone. Reduction with $LiAlH_4$ cleanly converted **10** to brexan-2-ol (**11**), which was readily reoxidized

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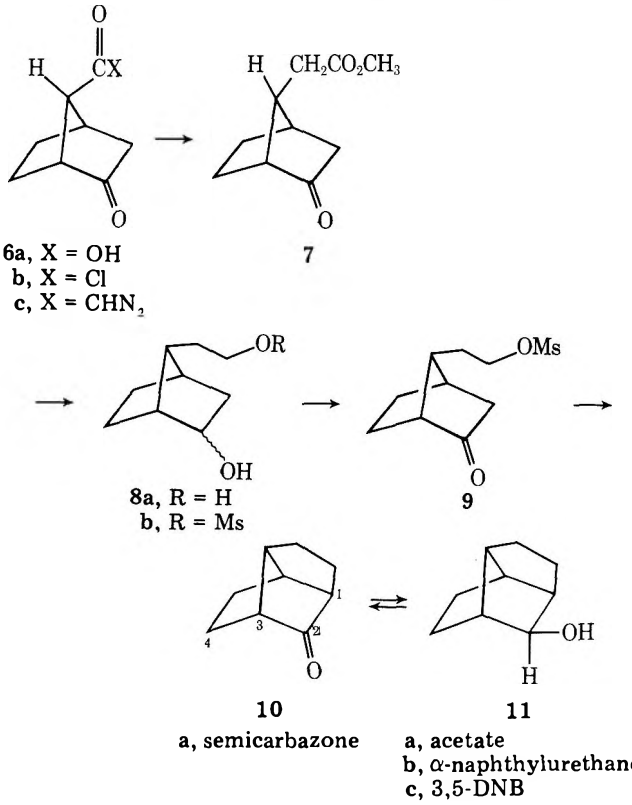
Scheme II. Synthesis of Brexan-2-ol



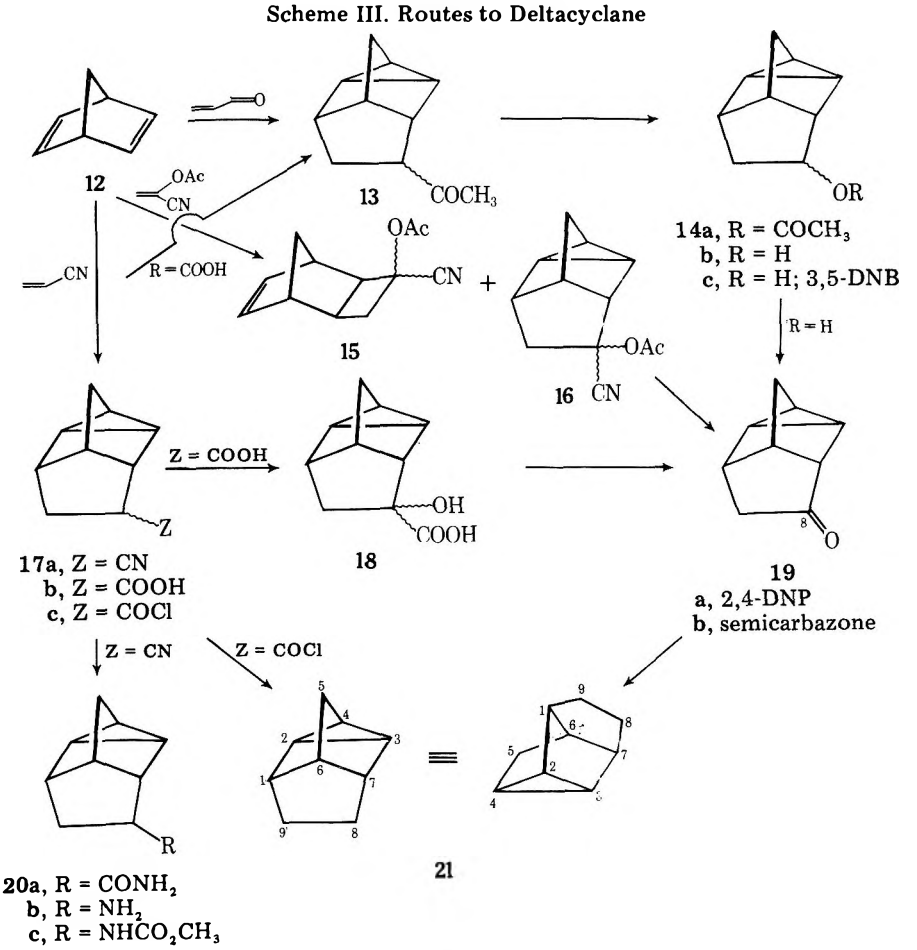
to the ketone. The overall yield in the eight-step sequence **6** → **11** was 6% and was not optimized. Brexan-2-ol (**11**) is crystalline, as are its α-naphthylurethane and 3,5-dinitrobenzoate, but its acetate **11a** (readily obtained with Ac_2O/Py) is liquid. Independent proofs of structure for brexan-2-one are described later in part V.

II. Routes to Deltacyclane.[7] This mesoid hydrocarbon (**21**) was pivotal in our synthetic plans for two reasons. Its tetracyclic skeleton seemed rather directly accessible by homoconjugative Diels–Alder reactions of norbornadiene (e.g., **12** → **17a** had been reported[8]), and electrophilic cleavage of its two types of cyclopropyl bonds could produce functionalized brendanes (e.g., rupture of the 2,3 bond) and/or brexanes (e.g., rupture of the 3,4 ≡ 2,4 bond). Scheme III outlines four routes we explored to deltacyclane, three of which aimed at ketone **19** as the penultimate goal.

Hall first reported the preparation of nitrile **17a**, in 12% yield, by [4 + 2] cycloaddition of norbornadiene (**12**) and acrylonitrile.[8] He converted the nitrile to the tetracyclic ketone **19** by a three-step sequence that involved hydrolysis to the carboxylic acid **17b** (44%), permanganate oxidation to hydroxy acid **18** (17%), and dichromate oxidation to ketone **19** (33%). We obtained this ketone by Hall's route, but in our hands the oxidation steps gave yields that were variable and frequently even lower than those reported.

We also applied Wiberg's[9] general method of decarboxylation to convert acid **17b** to deltacyclane **21**. In this sequence, without purification of intermediates, the acid chloride **17c** was prepared ($SOCl_2$/Py) and converted to the corresponding *tert*-butyl peroxyester by action of *tert*-butyl hydroperoxide. Thermolysis of the peroxyester in *p*-cymene gave deltacyclane (**21**), but its separation from *p*-cymene and from an unknown byproduct proved inefficient. We considered other ways to remove the CN group from **17a** such as conversion to NH_2 followed by reductive deamination.[10] The crystalline carboxamide **20a** was obtained conventionally from nitrile **17a** with H_2O_2. Although Hofmann rearrangement gave **20b** as a colorless liquid, this amine was not further investigated because it readily became colored in air, and its HBr and HCl salts were hygroscopic. Its urethane **20c**, however, was crys-

Scheme III. Routes to Deltacyclane



talline and stable, and served for characterization.

A more practicable synthesis of ketone **19** was developed from methyl ketone **13**, which in turn we prepared either by the action of methyllithium on acid **17b**, or by homoconjugative Diels–Alder addition of methyl vinyl ketone to norbornadiene (**12**). Both paths gave liquid ketone **13** as a mixture of two epimers in which the major component (configuration unassigned) predominates by a factor of ~1.6–2.6:1. Stereoisomerism at C-8 is of little consequence because that center becomes trigonal in ketone **19**. Therefore, the epimeric mixture was carried through the next two stages, viz. Baeyer–Villiger oxidation to acetate **14a** followed by saponification to alcohol **14b**. The oxidation succeeded with trifluoroperoxyacetic or *m*-chloroperoxybenzoic acid. Although deltacyclan-8-ol (**14b**) showed only one peak on gas chromatography, it still may consist of a mixture of epimers. A constant-melting 3,5-dinitrobenzoate (**14c**), however, probably represents a single stereoisomer. Brown's reagent readily oxidized **14b** to liquid ketone **19**, which gives crystalline derivatives **19a** and **19b**.

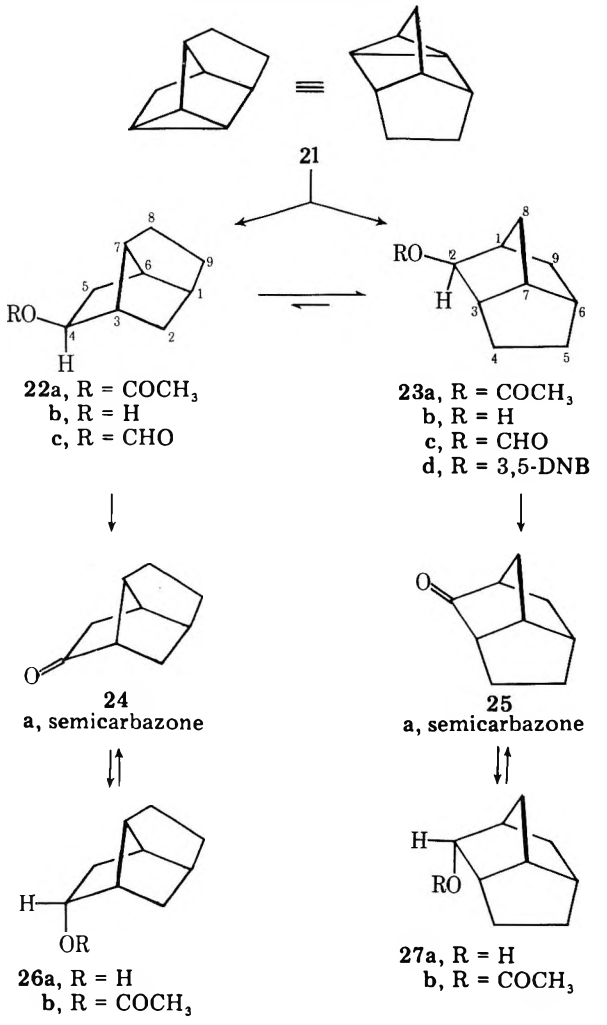
Our shortest route to deltacyclan-8-one (**19**) involved thermal cycloaddition of norbornadiene (**12**) and α-acetoxyacrylonitrile to produce a mixture of cyanohydrin acetates (**15** + **16**) in 28% yield. The presence of **15** as a minor component was inferred when saponification produced a 1:4 mixture of ketones, whose IR showed carbonyl absorption at 1770 cm^{-1} (cyclobutanone) as well as the 1740-cm^{-1} band for the major ketone, deltacyclan-8-one (**19**).[11a] The minor ketone, which still contains an olefin link, was removed by extraction with aqueous silver nitrate. Ketone **19** (and its semicarbazone **19b**) was reduced to liquid deltacyclane (**21**) by modified Wolff–Kishner methods.

III. Synthesis of Brex-4-yl and Brend-2-yl Systems. The cyclopropyl ring in deltacyclane (**21**) cleaves readily at room temperature in acetic acid/sulfuric acid. The products are *exo*-4-brexyl acetate (**22a**) and *exo*-2-brendyl acetate (**23a**), and the proportion of the latter acetate increases with time (Scheme IV). E.g., the brendyl/brexyl ratio (i.e., **23a**/**24a**) was about 1.5 after 20 min, but progressively increased to about 49 after 92 h. Clearly, the brendyl skeleton is the more stable, and the acid medium allows interconversion through a Wagner–Meerwein shift in their corresponding cations (viz. **3** → **4**). An acetate mixture from a 20-min run was separated by preparative gas chromatography and afforded **22a** and **23a** as clear liquids. Each acetate was readily saponified to its crystalline alcohol (**22b** and **23b**, respectively).

When our immediate objective was to prepare only the brend-2-yl compounds, we found it better to open deltacyclane in formic acid/sulfuric acid. After 20 h at room temperature, the formate esters **23c** and **22c** were present in the mixture in a ratio of ~50:1. Direct saponification gave crystalline *exo*-brendan-2-ol (**23b**) sufficiently pure (~95%) to carry forward. Acetylation of **23b** with Ac_2O/Py gave liquid **23a**, identical with that from the acetolysis route, and the 3,5-dinitrobenzoate derivative (**23d**) was crystalline.

The ketones **24** and **25** could be obtained individually by Brown oxidation of their respective pure exo alcohols. But we found it more practicable to prepare a mixture of the two ketones (by acetolysis of deltacyclane followed directly by saponification and oxidation) and then to separate them by preparative gas chromatography. Brexan-4-one (**24**) is a liquid, whereas brendan-2-one (**25**) is solid. Both show an infrared carbonyl band typical of a cyclopentanone (1745–1747 cm^{-1}), and brexan-4-one also absorbs at 1405 cm^{-1}, consistent with the presence of a $-CH_2CO-$. Both ketones were further characterized as their crystalline semicarbazones **24a** and **25a**. Evidence for location of the carbonyl groups as well as independent structural proof for the brexyl and brendyl skeletons are presented later in part V. The individual ketones were

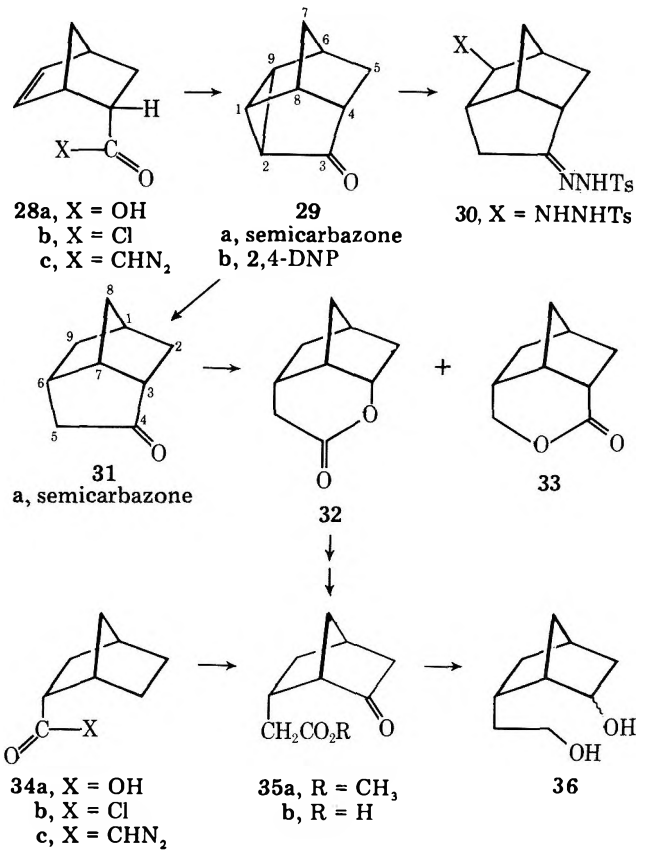
Scheme IV. Synthesis of Brex-4-yl and Brend-2-yl Systems



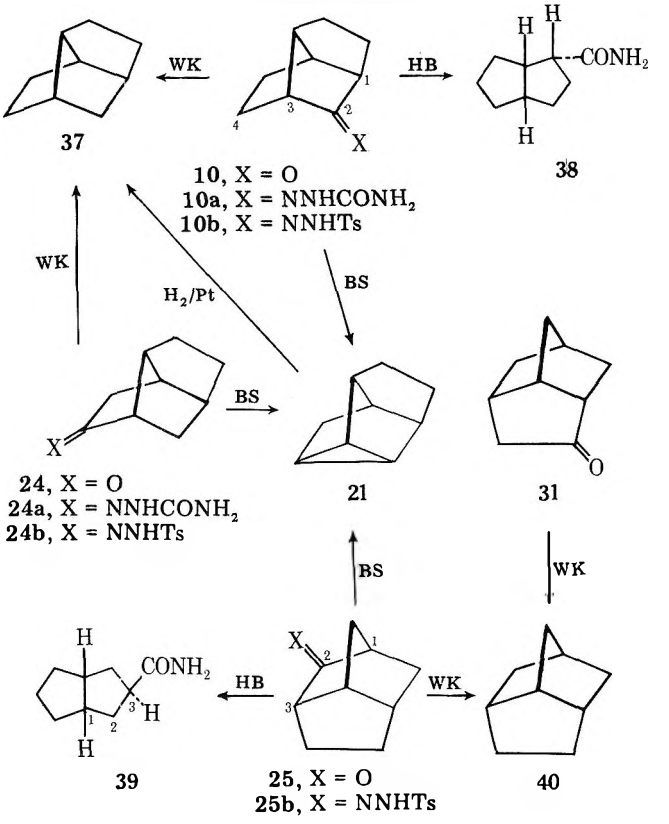
reduced with lithium aluminum hydride to the corresponding endo alcohols (liquid **26a** and solid **27a**), each of which was reoxidized to its parent ketone and readily acetylated (Ac_2O/Py) to acetates **26b** and **27b**, respectively.

IV. Synthesis and Structure Proof of Brendan-4-one (31). We found a convenient entry to the brendane system functionalized at C-4 from *endo*-5-norbornene-2-carboxylic acid (**28a**). This acid was converted to its acid chloride (**28b**) with oxalyl chloride and then to its diazomethyl ketone (**28c**) with diazomethane (Scheme V). Both **28b** and **28c** were liquids and were handled without purification. Intramolecular carbenoid addition of the diazomethyl group was effected with copper bronze, which gave the crystalline tetracyclic ketone **29** in an overall yield of 31% from **28**. Characteristic spectral features of this rigid, cyclopropyl ketone included a cyclopropyl C–H stretching band at 3048 cm^{-1}, a carbonyl stretching band at 1734 cm^{-1}, and UV λ_{max} (EtOH) 271 nm (ε 50). Ketone **29** gave a semicarbazone (**29a**) and a 2,4-dinitrophenylhydrazone (**29b**), whose analytical and spectral data indicated they were conventional derivatives. Interestingly, however, an unexpected result occurred on attempted routine preparation of a *p*-toluenesulfonylhydrazone. The derived product had combined with two molecules of the tosylhydrazine reagent and was soluble in dilute hydrochloric acid. We tentatively assign structure **30** to this bisfunctionalized product and presume it arises by a Michael-like addition to the "conjugated" cyclopropyl ketone, with cleavage of the more strained "conjugated" bond. This regioselectivity in cleavage is observed in the next synthetic step, opening of **29** to the target ketone **31**, either by catalytic hydrogenation (Pd/C) or by Li/NH_3 reduction. The crude brendan-4-one

Scheme V. Synthesis and Structure Proof of Brendan-4-one



Scheme VI. Structural Correlations in Brexyl and Brendyl Systems



(~86–89% yield) may be purified through a sodium bisulfite addition product or through hydrolysis of its high-melting semicarbazone (**31a**). Pure brendan-4-one shows carbonyl absorption at 1744 cm^{-1} (with slight splitting at 1703) and a methylene bending vibration at 1407 cm^{-1} characteristic of a $-CH_2CO-$ unit. Both enolizable hydrogens were exchanged completely by deuterium on reflux in $MeOD/D_2O$ containing K_2CO_3. To rule out the possibility of unexpected molecular rearrangements, we carried out an independent proof of structure for ketone **31** as follows.

Baeyer–Villiger oxidation of **31** with trifluoroperoxyacetic acid gave a mixture of the two δ-lactones **32** and **33**. We could not separate them directly, but found that saponification of the mixture followed by acidification at 0 °C regenerated lactone **33** and left the other component as the hydroxy acid. Without separation this mixture was treated with diazomethane, oxidized with Brown's reagent, and again saponified and acidified to reclose lactone **33**. An alkaline extraction readily separated lactone **33** from keto acid **35b**, and each was purified and characterized. Diazomethane converted **35b** to a pure sample of keto methyl ester **35a**. And this liquid ester was identical (IR and ^1H NMR) with authentic material that we synthesized from known keto acid **34a** by a three-step Arndt–Eistert homologation via acid chloride **34b** and diazomethyl ketone **34c**. The keto ester **35a** was reduced with $LiAlH_4$ to a crystalline diol (**36**), which probably has an *endo*-OH but for which we have no positive evidence.

V. Structural Correlations in Brexyl and Brendyl Systems. Because the brexyl and brendyl ketones in Schemes II–V play key roles in a variety of mechanistic studies, we wanted to confirm their structures by independent means. We used Haller–Bauer (HB) reactions, Wolff–Kishner (WK) reductions, and carbene insertions via Bamford–Stevens (BS) reactions as summarized in Scheme VI.

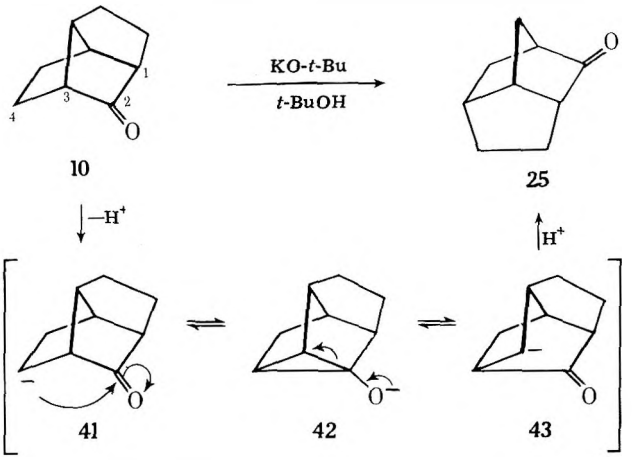
Haller–Bauer cleavage of the nonenolizable brexan-2-one (**10**) with sodium amide in diisopropyl ether produced *cis*-bicyclo[3.3.0]octane-*cis*-2-carboxamide (**38**). The melting point (161 °C), mixture melting point, and infrared absorption of this amide were identical with those of an authentic sample.[12]

A similar Haller–Bauer reaction opened brendan-2-one (**25**). Unlike the symmetrical brexan-2-one, however, brendan-2-one has two bonds that could potentially rupture, viz. 1,2 or 2,3. After repeated recrystallization of the crude cleavage product, we isolated an amide whose melting point (136–137 °C) agrees with that reported[13] for **39**, in which the H at C-3 is trans to the angular hydrogens. The cis epimer of **39** is reported to have mp 153 °C. Since C-2–C-3 cleavage of **25** should produce the cis geometry initially, we infer that the $CONH_2$ group epimerized in the alkaline medium. This inference is reasonable because Granger et al. have shown for the *cis*-bicyclo[3.3.0]octane skeleton that a CO_2CH_3 group at C-3 is more stable in the configuration corresponding to **39** than in the epimeric one.[13]

That brexan-2-one (**10**) and brexan-4-one (**24**) have identical carbon skeletons was shown by Wolff–Kishner reductions of their corresponding semicarbazones (**10a** and **24a**) to the same liquid tricyclic hydrocarbon, brexane (**37**). Likewise, Wolff–Kishner reductions of brendan-2-one (**25**) and brendan-4-one (**31**) produced the same crystalline hydrocarbon, brendane (**40**).

Finally the three ketones **10**, **24**, and **25** were interrelated with one another and with deltacyclan-8-one (**19**) by preparation of their corresponding *p*-toluenesulfonylhydrazones (**10b**, **24b**, and **25b**, respectively), followed by thermolysis (~150–160 °C) of their sodium salts in aprotic solvent (Bamford–Stevens reaction). Each substrate was converted to the same hydrocarbon, deltacyclane (**21**). In aprotic media such thermal Bamford–Stevens reactions produce carbenes and, for the cases at hand, these carbenes form the cyclopropyl ring in deltacyclane by 1,3 insertion. Hydrogenation of hydrocarbon **21** with Pt in acetic acid at 95 °C produced brexane (**37**), as well as brendyl and brexyl acetates from electrophilic ring cleavage.[14]

Scheme VII. Skeletal Isomerization via Homoenolate Ions



VI. Skeletal Isomerization via Homoenolate Ions. The nonenolizable nature of the brex-2-yl and brend-2-yl ketones and their structural relationship to each other led us to explore homoenolization to isomerize ring skeletons.[15] We found that prolonged treatment of brexan-2-one (**10**) in KO-*t*-Bu/*t*-BuOH at 185 °C transformed it to brendan-2-one (**25**). The change (Scheme VII) is interpreted as an abstraction of a C-4 proton in **10** to produce the homoenolate ion **41**, which is either in equilibrium with species **42** and **43** or is a resonance contributor to a hybrid ion represented by **41**, **42**, and **43**. In any case protonation at the negative site in **43** gives brendan-2-one. To learn if brendanone could be partially reverted to brexanone, we treated **25** similarly with KO-*t*-Bu. The product contained no detectable brexanone (**10**), and consisted of starting ketone **25** with 4% of an unidentified contaminant. The driving force for the **10** → **25** isomerization lies, very likely, in the greater stability of the brendyl ring system. E.g., we noted earlier (Scheme IV) that *exo*-brend-2-yl acetate (or formate) is favored at equilibrium over the *exo*-brex-4-yl isomer by a ratio of nearly 50:1. And recent molecular mechanics calculations suggest an enthalpy difference of ~2.90 kcal/mol (12.1 kJ/mol) for the parent hydrocarbons brendane and brexane.[16] The ability to interconvert polycyclic ketones under alkaline conditions should be especially useful for optically active substrates. Thus, e.g., optically active brexan-2-one should produce optically active brendan-2-one with no attendant racemization and with predictable relative chirality.

Experimental Section

General. Melting points are corrected and rounded to the nearer half degree. Boiling points are uncorrected and refer to atmospheric pressure unless stated otherwise. Infrared band positions are calibrated and are expressed in reciprocal centimeters; the letters w, m, s, br, and sh refer to weak, medium, strong, broad, and shoulder, respectively. Proton magnetic resonance spectra were recorded on a 60-MHz instrument (Varian A-60) with internal tetramethylsilane as a standard. All chemical shifts are expressed in δ units and s, d, t, and m refer to singlet, doublet, triplet, and multiplet, respectively. Ultraviolet spectra were recorded on Beckman DK-2 or on Cary Model 14 recording spectrophotometers with 1-cm quartz cells. Gas chromatographic analyses (GLC) were performed on a Perkin-Elmer Model 226 Analytical instrument with a hydrogen flame ionization detector. Preparative GLC was done on a Wilkens Aerograph "Autoprep" Model A-700, with a thermal conductivity detector. The carrier gas was always helium. The following column designations are used. Model 226: Golay R, 150-ft Golay column (0.01-in. i.d.) with polypropylene glycol liquid phase (UCON-oil, LB-550-X); Golay Z, 200-ft Golay column (0.01-in. i.d.) with SE-30 silicone gum rubber liquid phase; Golay MBMA, 150-ft Golay column (0.01-in. i.d.) with 80% *m*-bis(*m*-phenoxyphenoxy)benzene plus 20% alumina-washed Apiezon-L; Golay Castorwax, 200-ft Golay column (0.02-in. i.d.), Castorwax liquid phase; Carbowax, 9-ft packed column (⅛-in. o.d.); Squalane, 9-ft packed column (⅛-in. o.d.), 15% squalane liquid phase on Chromosorb W support. Model A-700: Carbowax, 20 ft × ⅜ in. packed column with 30% Carbowax 20-M on Chromosorb W support; SE-30, 20 ft × ⅜ in. packed column with 30% SE-30 silicone gum rubber on Chromosorb P support; Castorwax, 20 ft × ⅜ in. packed column with 20% Castorwax on Chromosorb P support. The column designation and column temperature are reported for each GLC.

Mass spectra were recorded with a Consolidated Electrodynamics Corp. Mass Spectrometer Type 21-103C. Elemental analyses were performed by Mr. Joseph Walter of this Department.

"Semicarbazide acetate" solution was prepared from powdered semicarbazide hydrochloride (25 g), which was combined with powdered sodium acetate trihydrate (40 g). Methanol (75 mL) was added to the paste, and the slurry was stirred and allowed to stand overnight. The solid was collected and washed with methanol (25 mL). The filtrate and washings (~140 mL total) was the solution used for the preparation of semicarbazones.

For chromatography commercial pentane, hexane, and petroleum ether were first purified by 24 h of treatment with ca. one-third of its volume of a solution of 50% sulfuric acid and 50% fuming sulfuric acid. The hydrocarbon layer was washed with water, dried over magnesium sulfate, passed through a column of alumina (Alcoa), and distilled. Diethyl ether and diisopropyl ether were dried by distillation from lithium aluminum hydride. Benzene was dried over molecular sieves followed by distillation under nitrogen. Pyridine was dried by distillation of reagent grade material from barium oxide under nitrogen. Deuterium oxide (>99.5% d_2) was obtained from General Dynamics Corporation. Methanol-*O*-*d* was from Merck Ltd. of Canada and was >95% d_1. "Copper bronze" powder (lot no. 3165) was grade MD 101 and was kindly provided by the Metals Disintegrating Division of the Martin-Marietta Corporation, Elizabeth B, New Jersey. Solvent evaporations in vacuo were done on a rotary evaporator and refer to ~15-mm aspirator pressure.

2-Oxo-*syn*-7-bicyclo[2.2.1]heptanecarboxylic Acid (6a). A mixture of the exo and endo isomers of 2-bicyclo[2.2.1]hept-5-enecarboxylic acid (100 g, 0.72 mol, Aldrich Chemical Co.) was converted via lactones to *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylic acid in a manner similar to that reported by Beckman and Geiger[17] except that we handled much larger batches. All details are available in the Ph.D. dissertation of Swartz.[18] Beckman and Geiger oxidized the hydroxy acid to the desired keto acid (41% yield) with alkaline permanganate; however, we developed the following improved method. Crude hydroxy acid (78.0 g, 0.5 mol, mp 145–150 °C (reported[17] 155–157 °C)) was esterified with ethereal diazomethane[19] and the resulting ether solution of the ester [ν (neat) 3436, 1730 cm^{-1}] was filtered and treated with the Brown[20] oxidation reagent (500 mL; 1.0 mol) over a 30-min period. After an additional 16 h at room temperature, the stirred, two-layer mixture was diluted with water, and the water layer was extracted with ether. The combined ether layers were washed with saturated sodium bicarbonate and on workup left 73.4 g (87%) of yellow, liquid keto ester. Gas chromatography (Golay Castorwax, 150 °C) showed two minor impurities that totaled <5%. The keto ester was refluxed 2.5 h in a solution made up from potassium hydroxide (35 g) in 1 L of 75% aqueous methanol (v/v). Most of the methanol was removed on a rotary evaporator and the solution was made slightly acidic with dilute sulfuric acid. Addition of brine and thorough extraction with ether gave 64.9 g (97%) of the desired keto acid: mp 120.5–122.5 °C (reported[17] 122–123 °C). Our product was 97% pure as indicated by GLC (Golay R, 145 °C, 39 psi He) on a small sample esterified with diazomethane.

Methyl 2-Oxo-*syn*-7-bicyclo[2.2.1]heptaneacetate (7) by Arndt–Eistert Homologation. (a) Preparation of Sodium Salt. Distilled water (200 mL) was carefully added to a mixture of keto acid **6a** (38.5 g, 0.255 mol) and anhydrous sodium bicarbonate (21.3 g, 0.255 mol), and the solution was shaken occasionally for 2 h until CO_2 evolution had ceased. Most of the water was removed by rotary evaporation, dry benzene was added, and the benzene–water azeotrope was removed on the rotary evaporator. The solid sodium salt was triturated several times with ether and dried in a vacuum oven at 94 °C for 10 h; 43.8 g (99%).

(b) Conversion to Acid Chloride (6b). Oxalyl chloride (59.5 g, 0.47 mol, Aldrich Chemical Co.) in dry ether (200 mL) was added dropwise during 30 min to a magnetically stirred, cooled (0 °C) suspension of the keto acid sodium salt (43.8 g, 0.25 mol) in dry ether (1.5 L). The evolved gases (CO_2 and CO) escaped through a drying tube on the condenser. After an additional 1.5 h at 0 °C, the stirred mixture was filtered under vacuum through a cotton plug to remove suspended sodium chloride, and the ether was evaporated on a rotary evaporator, with moisture excluded. Dry benzene (50 mL) was added, and further evaporation removed both the benzene and any remaining oxalyl chloride. The cloudy, liquid keto acid chloride (**6b**, 37.8 g, 88%) showed the expected carbonyl bands [ν (neat) 1801, 1749 cm^{-1}] and was used without further purification.

(c) Preparation of Diazo Ketone (6c). The acid chloride **6b** (37.8 g, 0.22 mol) in dry ether (150 mL) was added slowly to an excess of ethereal diazomethane,[19] which was cooled in ice and rapidly stirred magnetically. During addition pale-yellow keto diazo ketone precipitated, as N_2 and CH_3Cl were evolved from solution. Stirring at 0 °C was continued 30 min after addition was completed, and the ether was aspirated to leave the 2-oxo-*syn*-7-diazomethyl ketone **6c:** 36.8 h, 94.5%; mp 100–105 °C (softens at 95 °C); IR ν (CCl_4) 3116 (m, CH of diazo ketone), 2108 (s, diazo unit), 1754 (C=O cyclopentanone), 1648 (C=O of diazo ketone unit). The entire batch was dissolved in a minimum amount of dry benzene and precipitated with *n*-pentane. The first crop (27.6 g, 71%, mp 106–107 °C) was pure enough to use in the next step. An analytical sample was obtained as pale-yellow crystals by recrystallization from benzene–pentane: mp 106.5–107.5 °C (gas evolved, softens at 105 °C).

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.31; H, 5.70.

(d) Wolff Rearrangement. Silver benzoate was prepared from equimolar amounts of benzoic acid and silver nitrate in water and was dried overnight in a vacuum oven at 90 °C. The dry brown salt (10 g, 0.04 mol) was dissolved in trimethylamine (92 g, 0.91 mol, Eastman, undistilled but clear) and the dark mixture was filtered by gravity to give a yellow solution of the silver benzoate–triethylamine catalyst.[21] A few drops of catalyst solution was added to a stirred solution of the keto diazo ketone (25.0 g, 0.14 mol; mp 106–107 °C) in dry methanol (570 mL). Nitrogen was evolved slowly but steadily as the color deepened and colloidal silver formed. Stirring was continued at room temperature and more catalyst solution was added whenever gas evolution became slow. After addition of ~20 mL of catalyst (over 12 h) the mixture was refluxed for 20 min and gravity-filtered, and the methanol was removed on a rotary evaporator. The residue was taken up in 250 mL of ether, which was then filtered and washed successively with 5% sulfuric acid (3 × 20 mL), 5% sodium bicarbonate (2 × 20 mL), and brine (2 × 20 mL), and was treated with activated charcoal, dried ($MgSO_4$), and evaporated. The yellow, viscous liquid (22.4 g, 88%) was vacuum distilled. A middle fraction [bp 100 °C (0.2 mm)] consisted of 17.7 g (69.5%) of colorless liquid keto ester **7**, shown by GLC (Golay Castorwax, 150 °C) to be >99% pure; n^{23}_D 1.4803; IR ν (neat) 1736 (s, ester C=O), overlapped with 1748 cm^{-1} (s, ketone C=O); ^1H NMR ($CDCl_3$) δ 3.70 (s, 3, OCH_3), 2.65–1.40 (m, 11). The overall yield of **7** from **6** was 43%.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.70; H, 7.85.

2′-(*syn*-7-Bicyclo[2.2.1]heptan-2-ol)ethanol (8a). The homologated keto ester **7** (16.4 g, 0.09 mol) in dry ether (100 mL) was added dropwise over 1 h from a pressure-equalizing funnel to a magnetically stirred, cold (5 °C) suspension of $LiAlH_4$ (22.7 g, 0.80 mol) in dry ether (500 mL). The mixture was stirred 12 h at room temperature and then was successively treated dropwise with water (23 mL), 15% sodium hydroxide (23 mL), and water (68 mL). After an additional hour the granular inorganic solid was separated. Workup of the ether left a viscous, liquid mixture of epimeric diols (**8a**, 14 g, 98%): IR ν (neat) 3500–3100 (s, br, OH), 1095 (m), 1038 (m), 1008 cm^{-1} (m). For analysis a small amount was distilled twice in a vacuum sublimation apparatus [bath temperature 95–100 °C (0.25 mm)]. The center cut of the colorless liquid was dried under vacuum (0.25 mm) for 24 h at room temperature and 12 h at 40 °C: GLC (Golay Z, 120 °C) showed two peaks in the ratio 108:1 (t_R ~29 and 42 min, respectively); ^1H NMR ($CDCl_3$) δ 4.88–3.45 (m, 6), 2.45–0.73 (m, 10).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.89; H, 10.42.

Diol Monomesylate 8b. A solution of methanesulfonyl chloride (6.9 g, 0.06 mol, bp 162 °C) in dry pyridine (30 mL) was added to a cold (5 °C) solution of diol **8a** (9.9 g, 0.056 mol) in dry pyridine (40 mL). Pyridinium hydrochloride formed immediately in the orange reaction mixture, which was stirred 10 h in a cold room (5 °C). Water (1 mL) was added and after 30 min the mixture was poured into cold water and worked up with ether, which was washed in turn with cold 5% hydrochloric acid (5 × 40 mL), cold 5% sodium bicarbonate (40 mL), and cold brine (40 mL). The ether layer was concentrated to ~50 mL in a rotary evaporator, and this solution of the diol monomesylate was used directly in the next step. For spectral analysis a portion of the ether was dried over $MgSO_4$ for 30 min at −5 °C and evaporated in vacuo to leave **8b** as an oil: IR ν (neat) 3542 and 3391 (m, br, OH), 3020 (w, CH), 1353 and 1172 (s, sulfonate ester), 975 (m), 946 (m), 917 cm^{-1} (m).

7-*syn*-(2′-Mesyloxyethyl)bicyclo[2.2.1]heptan-2-one (Keto Mesylate 9). Brown's oxidation reagent (56 mL, 0.11 mol)[20] was added to the stirred ether solution of the diol monomesylate **8b**, all maintained at 5 °C in a cold room during addition and for 10 h thereafter. Conventional workup and removal of the ether on a rotary evaporator left the keto mesylate **9** as a slightly yellow oil (5.9 g, 45% from **8**): IR ν (neat) 3022 (m, CH), 1744 (s, C=O), 1352 and 1175 (s, sulfonate ester), 974 (s), 943 (s), 918 cm^{-1} (s). This product was used in the next step without purification. A sample in ether solution stored in the refrigerator for 6 months underwent little deterioration, based on infrared inspection.[22]

Tricyclo[4.3.0.0^{3,7}]nonan-2-one (Brexan-2-one) (10). Sodium hydride sand was prepared in a drybox under N_2 by repeated pentane trituration of a 50% suspension of sodium hydride in mineral oil (Metal Hydrides, Inc.) followed by collection on a filter funnel and thorough washing with dry pentane. The gray solid was dried under vacuum and stored in a desiccator. A solution of keto mesylate **9** (5.9 g, 0.025 mol) in dry, distilled *N,N*-dimethylformamide (100 mL, bp 153 °C) was degassed with a stream of nitrogen, and dry sodium hydride sand (2.4 g, 0.10 mol) was added all at once. After most of the gas evolution ceased (30 min), the flask was lowered into an oil bath (60 °C) and the brown mixture was stirred magnetically for 11 h. The excess of NaH was decomposed by careful, dropwise addition of methanol, and after an additional 1 h the stirred mixture was poured into water (300 mL) and extracted with pentane (5 × 50 mL), which was then washed with 5% hydrochloric acid and brine, and dried ($MgSO_4$). GLC at this stage (Golay R, 145 °C) showed the brexan-2-one to be 96% pure. The pentane solution was concentrated to 25 mL on an 18-in. spinning band distillation column with a 10:1 reflux ratio, and the ketone was isolated as a colorless, pure liquid (1.05 g, 32%) by preparative GLC (Carboxwax, 222 °C) with collectors cooled in dry ice–acetone. For elemental analysis the brexan-2-one was vacuum distilled [bath at 120–125 °C (35 mm)]: n^{26}_D 1.4951; M$^+$/*e* 136, prominent *m/e* peaks at 67 (100), 70 (40), 79 (79), 80 (99); IR ν (neat) 3466 (w, C=O overtone), 1841 (w) and 1746 (s, C=O), 1069 (s), 765 cm^{-1} (s); in CS_2 the C=O doublet is at 1844 (w) and 1748 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.31 (s, 4), 2.13–1.42 (m, 8). The ketone gave no precipitate when shaken at length with 40% aqueous sodium bisulfite and incorporated no deuterium when refluxed 7 days in D_2O/K_2CO_3.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.17; H, 9.07.

Brexan-2-one semicarbazone (10a) was obtained when the ketone (0.54 g) was heated in a methanolic semicarbazide acetate solution (see General) on the steam bath for 1 h, and then allowed to stand overnight. The derivative was precipitated with water, and the crude product (0.74 g) was recrystallized several times from hot methanol: 0.62 g; mp 188–189.5 °C; IR ν (KBr) 3475 (m), 3495 (m), and 3171 (s, NH), 1693 (C=O), 1580 cm^{-1} (C=N).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82. Found: C, 62.34; H, 7.89.

Tricyclo[4.3.0.0^{3,7}]nonan-2-ol (Brexan-2-ol) (11). Brexan-2-one (0.59 g, 0.0043 mol) in dry ether (25 mL) was reduced with $LiAlH_4$ (0.50 g, 0.013 mol) for 12 h at room temperature. The stirred solution was treated successively with water (0.5 mL), 15% sodium hydroxide (0.5 mL), and distilled water (1.5 mL). The ether was separated from the precipitated inorganic salts and, after workup and careful evaporation, left white brexan-2-ol (0.59 g, 98%); one vacuum sublimation [bath 55–65 °C (12 mm)] gave 0.56 g, mp 84–86 °C. A second sublimation gave the analytical sample (mp 84.5–86.5 °C), which showed only one GLC peak (Golay Z, 100 °C): IR ν (CCl_4) 3626 (m, free OH), 3352 (m, bonded OH), 1080 (s), 1058 (s), 1008 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.71 (d, 1, J = 6 Hz, CHOH), 2.30–1.83 (m, 5), 1.80–1.22 (m, 8). A sharp spike at ~2.13 disappeared on addition of D_2O and likely was the OH.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.46; H, 10.11.

Conventional oxidation with Brown's reagent[20] or with activated manganese dioxide in petroleum ether (25 °C, 104 h) regenerated brexan-2-one.

2-Brexyl Acetate (11a). Brexan-2-ol (0.096 g, mp 81–82 °C) in freshly distilled acetic anhydride (4 mL) and dry pyridine (0.5 mL) was heated at 60–70 °C for 2 h and kept at room temperature for 14 h. After dilution with water and repeated extraction with pentane, the organic layer was washed successively with water, saturated sodium bicarbonate, and water, dried, and passed through a column of alumina (2 g) to remove any traces of alcohol. Careful aspiration of the pentane followed by three bulb-to-bulb distillations of the residue at 60–80 °C (3 mm) gave the pure acetate: n^{23}_D 1.4795; IR ν (CCl_4) 1735 (s), 1248 (s), 1046 (s), 1019 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 4.47 (d, 1, J = 5–6 Hz, CHO). The acetate was pure by GLC (Golay R, 145 °C), although at block temperatures of 240 °C some pyrolysis to deltacyclane occurs.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.21; H, 8.86.

Brexan-2-ol α-Naphthylurethane (11b). This derivative was

obtained when the alcohol (0.069 g) and α-naphthyl isocyanate (0.085 g) were heated on the steam bath for 20 min and allowed to stand overnight at room temperature. For analysis the derivative was recrystallized three times from 95% ethanol: white crystals; 0.094 g; mp 139–139.5 °C.

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89. Found: C, 78.37; H, 7.11

Brexan-2-ol 3,5-Dinitrobenzoate (11c). A pyridine solution of the alcohol and 1 equiv of 3,5-dinitrobenzoyl chloride (mp 67–69 °C) was stirred 10 h at room temperature. Conventional workup gave a crude solid (mp 104–130 °C), which was repeatedly recrystallized from benzene–hexane, followed by chromatography on alumina and a final recrystallization: feathery, pale yellow crystals; mp 136 °C (33%); ^{1}H NMR ($CDCl_3$) δ 4.82 (d, 1, J = 6 Hz, CHOCO).

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85. Found: C, 57.59; H, 4.91.

The parent alcohol was regenerated from this ester by saponification with KOH/methanol (10-h reflux) or by reduction with lithium aluminum hydride in ether.

8-Cyanotetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (17a). This nitrile was prepared from norbornadiene and acrylonitrile as reported by Hall:[8] bp 124–126 °C (16 mm); n^{24}D 1.5136; 15.1% yield [reported bp 124–126 °C (17 mm); n^{24}D 1.5053; 12.4% yield].

Tetracyclo[4.3.0^{2,4}.0^{3,7}]nonane-8-carboxylic Acid (17b). Hall's method was used to hydrolyze the nitrile to this carboxylic acid: bp 96–98 °C (0.1 mm); n^{24}D 1.4973; 18%.[8]

8-Hydroxytetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane-8-carboxylic Acid (18). Alkaline permanganate oxidation of **17b** as reported[8] gave hydroxy acid **18**, but our yields were variable (3.6%, mp 102–112 °C to 11.1%, mp 98–107 °C) and consistently lower than that reported (16.9%, mp 102–110 °C). We oxidized the hydroxy acid to deltacyclan-8-one (**19**) with dichromate as described, but obtained low yield (17–29%).

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane-8-carboxamide (20a). A solution of the nitrile **17a** (97.5 g), 30% hydrogen peroxide (200 mL), sodium hydroxide (6 N, 30 mL), and 95% ethanol (400 mL) was heated on the steam bath for 15 min then allowed to stand 45 min. More hydrogen peroxide (100 mL) was added and the mixture was heated for 1 h. The amide (65 g, mp 185–203 °C) was collected, washed with water and 95% ethanol, and dried in vacuo. Two recrystallizations gave mp 211–213 °C (48 g, 31%): IR ν (KBr) 3365 (s) and 3205 (s, NH), 3069 (m, cyclopropyl CH), 1655 (s) and 1627 (s, $CONH_2$), 790 cm^{-1} (s, cyclopropyl C–C deformation).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.76; H, 7.94.

Hofmann rearrangement[23] of amide **20a** (9.9 g) with sodium hydroxide (14.9 g) and bromine (3.6 mL) in water (120 mL) gave the primary amine **20b**, distilled as a colorless liquid: 2.8 g (34%); bp 80–82 °C (0.25 mm); with appropriate IR characteristics. However, the amine readily turned yellow on standing, and the hydrochloride and hydrobromide salts were hygroscopic and discolored.

8-(Carbomethoxyamino)tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (20c). A solution of sodium (4.6 g, 0.2 mol) dissolved in methanol (160 mL) was added to a stirred solution of amide **20a** (16.3 g, 0.1 mol, mp 211–213 °C) in methanol (100 mL) at 0 °C. After 20 min, bromine (16 g, 0.1 mol) was added at 0 °C during 15 min, and the solution was stirred 15 min at room temperature followed by 30 min on the steam bath. The mixture was cooled, the solvent was removed in vacuo, water (100 mL) was added, and the solid was collected and washed with water. One crystallization from absolute ethanol gave 13.8 g (72%), mp 78–83 °C. The analytical sample of the white urethane (from ethanol–water) had: mp 84.5–86 °C; IR ν (KBr) 3309 (m, NH), 3050 (w, cyclopropyl CH), 1720 (s, C=O), 800 cm^{-1} (m, cyclopropyl C–C deformation).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 78.37; H, 7.82. Found: C, 68.51; H, 7.93.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (Deltacyclane) (21) by Decarboxylation. Attempts to replace the carboxyl group of **17b** by halogen through the Hunsdiecker reaction[24] or the Cristol modification[25] of that reaction were unsuccessful. Wiberg's[9] three-step method for decarboxylation was tried, and provided deltacyclane in ~10% yield. Thionyl chloride (10.7 g, distilled) was added during 10 min to a stirred, cold (0 °C) solution of acid **17b** (15.0 g) and dry pyridine (7.13 g) in dry ether (100 mL). After an additional 1 h, the insoluble salts were filtered off and washed with dry ether. The ether filtrate provided 15.8 g of the oily acid chloride **17c**: IR ν (neat) 3051 (m, cyclopropyl CH), 1801 (s, C=O), 801 (s, cyclopropyl C–C deformation). Without purification the acid chloride (15.8 g) was added during 1.5 h to a stirred, cold (0 °C) solution of *tert*-butyl hydroperoxide (12.4 g, Lucidol Corp.) and dry pyridine (18.7 g) in *p*-cymene (62 mL; bp 175–176 °C, Fisher Certified). After an additional 1 h the stirred mixture was poured onto ice and the water was extracted with *p*-cymene, which was then washed successively with cold 8% sulfuric acid, ice water, 5% sodium bicarbonate, and ice water. The *p*-cymene solution containing the *tert*-butyl perester was dried over $MgSO_4$ for 1 h at 0 °C and was transferred to a flask equipped for distillation. The solution was heated until gas evolution began (145 °C). After 1 h at this temperature any distillate was returned to the solution, which was then distilled in portions through an 18-in. spinning-band column. Fractions collected between 120 and 175 °C (760 mm) totaled 3.41 g of liquid, which contained about equal amounts of deltacyclane, *p*-cymene, and an unknown compound, as revealed by gas chromatography (Golay Z, 95 °C) peak enhancement with authentic samples. We found it difficult to separate the deltacyclane efficiently from this mixture, and therefore alternative routes to the tetracyclic hydrocarbon were developed.

8-Acetyltetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (13). (a) By Addition of Methyllithium to Acid 17b.[26] A solution of methyllithium was prepared by addition, over 3 h, of methyl iodide (110 g) in dry ether (350 mL) to a suspension of lithium wire (14.8 g) in dry ether (350 mL). The filtered solution was added during 3 h to the carboxylic acid **17b** (30.0 g) in anhydrous ether (300 mL) at a rate that maintained gentle reflux in the stirred solution. After 30 min longer the mixture was poured into ice water (150 mL). Conventional workup of the ether (dried over $MgSO_4$) left 16.5 g of crude, liquid ketone. A portion (3.75 g) was chromatographed on alumina (120 g, Alcoa). Elution with petroleum ether containing 3–5% benzene gave 2.27 g of liquid, which was colorless after distillation: 2.01 g; bp 82–84 °C (1.2 mm); n^{28}D 1.4980; IR ν (neat) 3052 (m, cyclopropyl CH), 1706 (s, C=O), 1357 (m, CCH_3 deformation), 1168 (s), 802 cm^{-1} (s). Gas chromatography (Golay R, 140 °C) showed the two methyl ketone epimers **13** in a ratio of 2.6:1: ^{1}H NMR (neat) δ 3.25–2.73 (m, 1), 2.42–1.55 (m, 8, prominent $COCH_3$ singlet at 2.07), 1.47 (s, 2), 1.20–0.67 (m, 3, cyclopropyl H).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.55; H, 8.63.

(b) By Homoconjugative Diels–Alder Reaction. Commercial norbornadiene (500 g, Shell Corp.), methyl vinyl ketone (400 g, Monomer-Polymer Laboratories), and cupric acetate (2 g) were heated (200 °C) in a steel bomb for 12 h. The mixture was poured into hexane (5 L) and then filtered through Celite. The hexane was evaporated on the steam bath, and the residue was distilled to get a fraction (67 g), bp 60–90 °C (0.4 mm). A solution of this liquid in ether (600 mL) was extracted with 1.5 M aqueous silver nitrate solution (2 × 150 mL) and then with water (2 × 100 mL), dried ($MgSO_4$) overnight, and evaporated. The product was distilled through a Vigreux column and a fraction (46.8 g), bp 62–64 °C (0.4 mm), was collected. GLC (Golay R, 140 °C) revealed the two epimeric methyl ketones in a ratio 1.56:1. The infrared spectrum (neat) was the same, except for relative peak intensities, as that from the ketone epimers obtained by method a above. In a run where hydroquinone (~2 g) was used in place of the cupric acetate and the reaction was run at 188 °C and worked up by steam distillation (to remove bicycloheptadiene and to collect the 8-acetyldeltacyclane), a higher yield (74 g) of the product mixture was obtained. We also tried the homoconjugative Diels–Alder reaction catalyzed by $Ni(CN)_2{\cdot}2P(C_6H_5)_3$.[27]

In a run with norbornadiene (20 mL), methyl vinyl ketone (20 mL), and catalyst (0.65 g, mp 212 °C) in a sealed Pyrex tube at 120 °C for 15 h, we obtained 7 g of the epimeric ketones by steam distillation and ether extraction.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-8-ol (14b) by Baeyer–Villiger Oxidation.[28] **Method A.** A trifluoroperoxyacetic acid solution was prepared by dropwise (1.5 h) addition of trifluoroacetic anhydride (127 mL) at 0 °C to a stirred, cold suspension of 90% hydrogen peroxide (20.5 mL) in methylene chloride (130 mL). After another 15 min this cold (0 °C) solution was slowly (1 h) dropped into a stirred, cold (0 °C) suspension of 8-acetyldeltacyclane (**13**; 81 g, epimeric mixture) and anhydrous disodium hydrogen phosphate (35.5 g) in methylene chloride (500 mL). After an additional 20 min, the stirred suspension was refluxed 1 h and filtered, and the insoluble salts were washed with methylene chloride. The filtrate was washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation left a colorless liquid, which was distilled: 62.3 g; bp 54–60 °C (0.7 mm); IR ν (neat) 3053 (s, cyclopropyl CH), 1776 (m, C=O of $OCOCF_3$), 1734 (s, C=O of $OCOCH_3$), 1375 (m), 1357 (m), 1241 (s), 1027 (s), 803 (s, cyclopropyl C–C deformation). GLC (Golay R, 140 °C) showed two peaks in the ratio 1:20. This ester mixture (55.7 g) was refluxed for 3 h under nitrogen in a solution of potassium hydroxide (23 g) and methanol (250 mL). Evaporation of the methanol, addition of water, and extraction with ether gave on normal workup a colorless liquid, which was distilled: 41.7 g; bp 60–62 °C (0.5 mm); n^{23}D 1.5194; IR ν (neat) 3332 (s, br, OH), 3054 (cyclopropyl CH), 1072 (s), 1036 (s), 991 (m), 802 cm^{-1} (s, cyclopropyl C–C deformation). GLC (Castorwax, 174 °C) showed

only one peak, but the alcohol **14b** is likely a mixture of epimers.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.23; H, 8.72.

A **3,5-dinitrobenzoate (14c)** was prepared with anhydrous pyridine and 3,5-dinitrobenzoyl chloride. Several recrystallizations from 95% ethanol gave the analytical sample with constant mp 91.5–93 °C. This derivative probably represents a single epimer.

Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27. Found: C, 58.07; H, 4.34.

Method B. An epimeric mixture of methyl ketones (16.7 g, 0.10 mol) and *m*-chloroperoxybenzoic acid (33 g, 0.16 mol, Food Machinery Corp., 85% minimum purity) in methylene chloride (300 mL) was refluxed for 12 h. The solid *m*-chlorobenzoic acid was removed from the cold mixture and washed with methylene chloride, which was then extracted thoroughly with saturated sodium bicarbonate solution (3 × 300 mL) followed by brine (1 × 300 mL), and was filtered through dry, powdered sodium bicarbonate. Evaporation of the clear solution left 17.5 g (95.5%), and vacuum distillation [bp 88–90 °C (1.6 mm)] gave 14.6 g (81%) of the colorless, sweet-smelling acetates **14a**. The acetate mixture was saponified with potassium hydroxide (12.3 g) in methanol (135 mL) and water (12 mL). After 3 h at reflux and 15 h at room temperature the methanol was evaporated and the mixture was worked up conventionally with pentane. The colorless, tetracyclic alcohol **14b** was distilled: 19.2 g; bp 90–92 °C (1.4 mm). It remains liquid at room temperature, but partly solidified in the cold condenser.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonan-8-one (Deltacyclan-8-one) (19). Brown's oxidation reagent[20] (61 mL) was added during 20 min to a cold (0 °C) stirred solution of the liquid tetracyclic alcohol **14b** (15.0 g) in ether (50 mL). After 2 h at room temperature the ether layer was worked up normally, and the product on distillation gave a colorless liquid with a strong characteristic odor: 12.6 g (85%); bp 88–90 °C (11 mm); GLC (Castorwax, 162 °C) showed only one peak; IR ν (neat) 3068 (m, cyclopropyl CH), 1748 (s, C=O), 1405 (w, CH_2 α to C=O), 798 cm^{-1} (s, cyclopropyl C–C deformation). This spectrum was superimposable on that of an authentic sample of tetracyclic ketone **19** kindly supplied by Dr. H. K. Hall, Jr.[8] Oxidation of the alcohol **17b** with the Sarett reagent (CrO_3/Py)[29] also gave this ketone, but in lower yield (43%).

The **2,4-dinitrophenylhydrazone (19a)** precipitated when the ketone (0.05 g) and 2,4-dinitrophenylhydrazine (0.2 g) in ethanol (10 mL) containing concentrated hydrochloric acid (3 drops) sat overnight in the refrigerator: 0.11 g (93.5%); mp 189–191 °C. The analytical sample (from ethanol) had mp 193.5–194 °C.

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49. Found: C, 57.04; H, 4.42.

To get the **semicarbazone (19b)** the ketone (0.094 g) in methanol (2 mL) containing 3 drops of pyridine was treated with semicarbazide hydrochloride (0.222 g) in water (1.0 mL) on the steam bath for 5 min and then allowed to sit overnight in the refrigerator. This derivative (0.12 g, 89%, mp 209.5–211 °C) was recrystallized from methanol for analysis, mp 213.5–214 °C.

Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85. Found: C, 62.98; H, 6.65.

The parent ketone was regenerated when the semicarbazone was hydrolyzed with sodium hydroxide in water–ethanol.

Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane (Deltacyclane) (21) by Modified Wolff–Kishner Reduction.[30] Anhydrous hydrazine (45 mL, bp 113–114 °C, prepared by distillation of 95% hydrazine from an equal weight of potassium hydroxide) was added to deltacyclan-8-one (**19**; 13.4 g, 0.1 mol) dissolved in dry, freshly distilled diethylene glycol (150 mL). The mixture was refluxed 1 h and the excess of hydrazine was distilled out until the distillation temperature reached 220 °C. A solution of sodium (2.5 g) in diethylene glycol (90 mL) was added and when heating was resumed nitrogen started to evolve and the hydrocarbon distilled out continuously as it formed. Nitrogen evolution was almost quantitative and at the end of the reaction the distillation temperature rose to 230 °C. The condenser was washed with pentane, which was combined with the distillate, washed with water, dried (Na_2SO_4), and distilled at 760 mm. The deltacyclane, bp 152–153 °C, weighed 9.45 g (79%): n^{25}_D 1.4928; IR ν (neat) 3057 (m, cyclopropyl CH), 1306 (m, CH bend), 796 cm^{-1} (s, cyclopropyl C–C deformation); ^{1}H NMR (CS_2) δ 1.90 (s, 2), 1.70–1.42 (m, 7), 1.10–0.70 (m, 3, cyclopropyl H).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.91; H, 9.86.

Wolff–Kishner reduction of the semicarbazone (**19b**) of deltacyclan-8-one with sodium dissolved in diethylene glycol or with dry powdered KOH at 185–200 °C gave deltacyclane in lower yields (~50%). However, the KOH method has the attraction that the product distills from the reaction mixture directly in 95–98% purity.

Deltacyclan-8-one (19) from α-Acetoxyacrylonitrile. A mixture of norbornadiene (27.6 g, 0.33 mol), α-acetoxyacrylonitrile[31] (33.3 g, 0.3 mol), and hydroquinone (0.3 g) under nitrogen in a sealed *glass* tube was heated at 160 °C for 15 h. When cold, the dark brown mixture was poured into ether (600 mL), and the polymeric material that precipitated (12 g) was filtered off. The filtrate was evaporated and the residue was distilled in vacuo. Preliminary fractions [bp up to 165 °C (20 mm)] contained largely the starting reagents; the product was collected at bp 170–180 °C (20 mm), 17.2 g (28%). This mixture of isomeric cyanohydrin acetates in a solution of sodium hydroxide (30 g) in 10% H_2O–90% ethanol (300 mL) was refluxed 2 h. The mixture was steam-distilled until the distillate was clear (~300 mL), and the distillate was extracted with ether (4 × 75 mL), which was then washed with brine (2 × 75 mL), dried over Na_2SO_4, and evaporated. At this stage the residual liquid (7.2 g) showed two IR carbonyl bands (1740 and 1770 cm^{-1}) and consisted of a 4:1 mixture (GLC, 20% silicone grease, 190 °C) of deltacyclan-8-one (**19**) and the unsaturated cyclobutanone from a [2 + 2] addition pathway.

For separation of the two ketones, the mixture in pentane (30 mL) was vigorously extracted (10 min) with 25% aqueous silver nitrate (30 mL) and then again with 12% silver nitrate (40 mL). The pentane was then washed with water, dried with Na_2SO_4, and evaporated. Vacuum distillation of the residue gave pure (GLC) deltacyclan-8-one (**19**), 5 g, bp 88–90 °C (10 mm), identical with an authentic sample.[8] Overall yield from norbornadiene typically was 12–13%. (The silver nitrate extracts on workup gave 2.5 g of a mixture of the two ketones in ~1:1 ratio, by GLC.)

Acetolysis of Deltacyclane. Isolation of *exo*-4-Brexyl Acetate (22a). A mixture of deltacyclane (2.0 g), glacial acetic acid (100 mL), and 97% concentrated sulfuric acid (0.50 g) was stirred at room temperature. The mixture soon became homogeneous, and a brown color developed and gradually deepened. Aliquots were removed periodically and worked up by dilution with water and extraction with pentane, which was then washed with saturated sodium carbonate and water, dried over $MgSO_4$, and carefully evaporated at the water aspirator with no heat. GLC analysis (Golay R, 145 °C) showed that the ratio of *exo*-2-brendyl acetate/*exo*-4-brexyl acetate increased with time as follows: 1.5 (20 min); 2.3 (2.5 h); 2.9 (4 h); 49 (92 h). These ratios are based on peak heights only and are approximate. In all aliquots the starting hydrocarbon deltacyclane was evident in the GLC, but its proportion seemingly fluctuated with time. We also found that if the injection block temperature is too high (>220 °C) *exo*-4-brexyl acetate partly isomerizes to *exo*-2-brendyl acetate and partly decomposes to deltacyclane. (The brendyl acetate also pyrolyzes to deltacyclane at high block temperatures, but less readily.) Typically, the yield of mixed acetates from acetolysis was ~90%.

A mixture of the acetates (2.5 g; brendyl/brexyl ratio ~1.5) in pentane was separated by preparative gas chromatography (Autoprep-700, Carbowax, 165 °C, block 205 °C, He 195 cm^3/min, with sample injection directly onto the column with a 6-in. hypodermic needle. An early hydrocarbon fraction contained deltacyclane. The *exo*-2-brendyl acetate (t_R ~65 min) and *exo*-4-brexyl acetate (t_R ~80 min) were separately collected at dry ice–acetone temperature, and intermediate fractions were recycled. (Total recovery from preparative GLC 55–60%.) The liquid *exo*-4-brexyl acetate (**22a**) was >99.5% pure by analytical GLC (Golay R, 145 °C, block 200 °C): n^{25}_D 1.4798; IR ν (CCl_4) 1740 (s) and 1725 (sh, C=O), 1242 (s), 1215 (m), 1148 (m), 1057 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3, CH_3CO_2), 4.59 (d, 1, J = 6 Hz, CHO). The doublet has additional fine splitting.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 8.88.

The **exo-2-brendyl acetate (23a)** was >99.5% pure: n^{24}_D 1.4810; IR ν (neat) 1740 (s), 1730 (s, C=O doublet), 1380 (m), 1365 (m), 1245 (s), 1028 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 1, CHO). 1.95 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.55; H, 8.84.

***exo*-Brexan-4-ol (22b).** A solution of 4-brexyl acetate (0.030 g) and potassium hydroxide (0.35 g) in methanol (4 mL) and water (0.5 mL) was refluxed 5 h and then let stand at room temperature overnight. Addition of water, extraction with pentane, and normal workup gave, after one sublimation, white crystals (0.017 g, 72%), mp 51.5–53 °C. Resublimation for analysis gave: mp 52.5–53 °C; IR ν (CCl_4) 3595 (s), 1062 (s), 989 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) both before and after addition of D_2O, δ 3.71 (d, 1, J = 6 Hz, CHO; fine splitting is evident).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.35; H, 9.93.

***exo*-Brendan-2-ol (23b).** Pure *exo*-2-brendyl acetate was saponified in a solution of KOH (0.4 g) in methanol (7 mL) and water

(1 mL). After 6 h at reflux and 15 h at room temperature, the solution was diluted with water and worked up normally with pentane. The solid *exo*-brendan-2-ol was sublimed with water pump aspiration, mp 131–134 °C (0.68 g). Resublimation gave the analytical sample: mp 133.5–134.5 °C; IR ν (CCl_4) 3605 (s, free OH), 3525–3150 (br, bonded OH), 1150 (m), 1063 (s), 1021 cm^{-1} (s); ^1H NMR ($CDCl_3$) 3.30 (s, 1, CHO) before and after addition of D_2O.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.34; H, 10.20.

The 2-brendyl series is more efficiently arrived at by formolysis of deltacyclane as described below.

Formolysis of Deltacyclane. Preparation of exo-Brendan-2-ol (23b). A heterogeneous mixture of deltacyclane (0.95 g, ~90% pure), formic acid (45 mL, 97%) and concentrated sulfuric acid (0.20 g, 97%) was shaken at room temperature for 20 h. The homogeneous solution was diluted with water and worked up with pentane, which was washed successively with saturated sodium bicarbonate and water, dried ($MgSO_4$), and evaporated by water aspiration with no heat (0.88 g, 73%). GLC (Golay R, 145 °C) showed ~90% *exo*-2-brendyl formate and *exo*-4-brexyl formate in a ratio of ~50:1 (the brendyl ester has the shorter t_R) and minor peaks (total ~10%) due to deltacyclane and impurities. The formate mixture was saponified by 2 h of reflux in a solution of methanol (8 mL), water (1 mL), and potassium hydroxide (0.6 g). Dilution with water and normal pentane workup left the crude solid (0.72 g), which was sublimed at 12 mm (0.6 g, mp 87–95 °C). Recrystallization from the minimum amount of pentane or isooctane at dry ice temperature raised the melting point to 112–115 °C (sealed tube). Neither sublimation nor recrystallization (without severe loss) effectively removes residual *exo*-brexan-4-ol, small quantities of which are also difficult to detect by GLC. Nevertheless the purity of this *exo*-brendan-2-ol (~95%) is adequate for conversion to the acetate or the ketone, either of which is readily purified by gas chromatography.

The alcohol (0.1 g, mp 112–115 °C) was converted to its *acetate* **23b** in 96% yield by 2 h of reflux in acetic anhydride (4 mL, freshly distilled) and dry pyridine (0.5 mL). The acetate was worked up with pentane and distilled bulb-to-bulb, bp 60–80 °C (1 mm). It was identical in all respects with that obtained from the acetolysis route.

The **3,5-dinitrobenzoate** of *exo*-brendan-2-ol was prepared from the alcohol (0.6 g, mp 112–115 °C) and pure 3,5-dinitrobenzoyl chloride (0.20 g) in dry benzene (5 mL) and dry pyridine (0.75 mL) after 30 min of reflux. Normal workup gave: 0.13 g; 90%; mp 87–88 °C. The analytical sample of **23d**, repeatedly recrystallized from ethyl acetate–pentane, had: mp 98.5 °C; IR ν (CCl_4) 3080 (m), 1725 (s), 1485 (s), 1340 (s), 1275 (br), 1165 (s), 968 (m), 720 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 4.58 (s, 1, CHO).

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85. Found: C, 57.95; H, 5.01.

Brexan-4-one (24) and Brendan-2-one (25). Each of these ketones can be obtained by Brown oxidation of its respective pure exo alcohol. A more convenient route is as follows. A mixture (7.0 g) of 2-brendyl and 4-brexyl acetates (ratio 2.9:1) from acetolysis of deltacyclane was saponified by 27 h of reflux with KOH (22 g) in 95% ethanol (15 mL) and water (60 mL). Workup with water and ether gave 5.1 g (0.037 mol) (94%) of mixed alcohols, which was dissolved in ether (75 mL, previously treated with oxidizing agent to ensure inertness) and oxidized with the Brown reagent (37 mL, 0.074 mol). After 3 h at room temperature the heterogeneous mixture was worked up normally. Careful evaporation of the dried ether with a stream of dry N_2 and gentle heat left a waxy, white solid, 4.33 g (96%). The ratio of brendan-2-one and brexan-4-one was 2.6:1 (Golay R, 145 °C) and therefore there was no significant isomerization of ring skeletons during the oxidation. The ketones in pentane were separated[32] by preparative GLC (Autoprep-700, Carbowax, 160 °C, injector 205 °C, He 300 cm^3/min) and collected in receivers cooled in dry ice–acetone. Under optimum GLC conditions the total ketone recovery was as high as 70%.

The **brendan-2-one** was eluted first, and was camphorlike, mp 114–118 °C (1.27 g), pure by analytical GLC (Golay R, 145 °C). Two vacuum sublimations (water-pump) gave: mp 118.5–119.5 °C (softens 111 °C); IR ν (CCl_4) 1747 (s, C=O), 1169 (m), 1022 cm^{-1} (m); ^1H NMR δ 2.85–1.38 (m, 11), 1.10–0.75 (m, 1).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.57; H, 9.04.

The **semicarbazone** of **brendan-2-one** was obtained when the ketone in absolute methanol was heated for 3 min with semicarbazide acetate (2 equiv) reagent (see General) and let stand overnight at room temperature. Normal workup followed by recrystallization from water–methanol and finally from absolute methanol gave white, starlike crystals of **25a**, mp 159.5–162 °C.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.16; H, 7.82. Found: C, 62.08; H, 7.88.

The **brexan-4-one** (0.59 g) was liquid, and pure by analytical GLC: $n^{25}D$ 1.4968; IR ν (CCl_4) 1745 (s, C=O), 1405 (m, CH_2 α to C=O); IR ν (neat) 1744 (s), 1407 (m), 1161 (m), 1122 cm^{-1}; H NMR ($CDCl_3$) δ 2.45–2.03 (m, 6), 2.00–1.25 (m, 6).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.27; H, 8.73.

The **semicarbazone (24a)** of **brexan-4-one,** prepared as described above for the brendyl ketone, had mp 202–204 °C (from methanol).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.16; H, 7.82. Found: C, 62.21; H, 7.91.

Pure ketone **24** was regenerated when the semicarbazone (**24a,** 0.26 g), water (6 mL), and oxalic acid dihydrate (0.35 g) were heated together until 6 mL of distillate was collected. The distillate was worked up with pentane, and the product was distilled [bath 110–115 °C (15 mm)] to give 0.13 g of brexan-4-one, pure by GLC.

***endo*-Brexan-4-ol (26a).** Pure brexan-4-one (0.50 g) in dry ether (20 mL) was reduced with lithium aluminum hydride (2 g) in dry ether (125 mL) for 5 h at reflux. Workup as in the brendyl series gave a liquid alcohol (~92% endo, 8% exo by GLC on acetylated mixture) that was distilled at 60–80 °C (1.2 mm), 0.43 g, 85%. Sublimation onto a cold finger gave a white solid, which is a viscous liquid at room temperature: $n^{25}D$ 1.5100; IR ν (CCl_4) 3602 (s), 1123 (m), 1093 (s), 1078 (s), 1021 cm^{-1} (s); ^1H NMR ($CDCl_3$) before and after shaking with D_2O, δ 4.20 (m, 1, CHO). No epimeric exo alcohol was detectable by IR or NMR.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.10.

Oxidation of the alcohol (0.020 g) in ether (8 mL) with Brown's reagent[20] (1 mL) at room temperature for 6 h and normal workup regenerated the parent brexan-4-one (0.015, 80%, after one sublimation of the liquid on a cold finger).

***endo*-4-Brexyl Acetate (26b).** Pure *endo*-brexan-4-ol (0.11 g) was acetylated in acetic anhydride (4.5 mL) and pyridine (0.5 mL) at 60–70 °C for 2 h, and left at room temperature overnight. Conventional workup with water and pentane left the acetate, which was distilled twice bulb-to-bulb at 60–80 °C (2 mm); colorless, fragrant liquid (0.12 g, 80%); $n^{24}D$ 1.4807; IR ν (CCl_4) 1740 (s), 1725 (s), 1246 (s), 1238 (s), 1068 (s), 1037 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3, CH_3), 4.90 (m, 1, CHO).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.95; H, 8.75.

***endo*-Brendan-2-ol (27a).** A solution of brendan-2-one (0.17 g, mp 118 °C) in dry ether (10 mL) was added slowly to a stirred, ice-cooled suspension of powdered lithium aluminum hydride (0.60 g) in dry ether (100 mL). The mixture was refluxed 3 h and, when cold, was carefully treated with saturated sodium sulfate (10 mL) to decompose the excess of hydride, followed by dilute sulfuric acid (10 mL, 2%). Normal workup of the ether layer left a solid (endo/exo ~95:5) that gave white crystals after sublimation: 0.5 g (84%); mp 165–166 °C (174–175 °C in a sealed capillary). Melting points can vary widely on a given sample owing to ease of sublimation and do not necessarily reflect variation in purity: IR ν (CCl_4) 3620 (s), 1112 (m), 1076 (s), 1056 cm^{-1} (m); ^1H NMR ($CDCl_3$) before and after shaking with D_2O, δ 4.11 (d, br, complex, 1, J = 8 Hz, CHO).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.31; H, 10.02.

Oxidation in ether with Brown's reagent[20] for 5 h at room temperature regenerated the parent ketone, mp 117–118 °C after sublimation.

***endo*-2-Brendyl Acetate (27b).** The endo alcohol (0.80 g, mp 155 °C) was heated at 60–70 °C for 2 h with freshly distilled acetic anhydride (3.5 mL) and dry pyridine (0.5 mL). After 48 h at room temperature the solution was again heated at 60–70 °C for 2 h. Ice water was added to the cooled solution and after a conventional pentane workup the colorless product was distilled twice (bulb-to-bulb) to furnish the sweet-smelling liquid acetate: $n^{22}D$ 1.4835; IR ν (CCl_4) 1738 (s), 1720 (sh), 1248 (s), 1052 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3, CH_3), 4.90 (d, br, complex, 1, J = 8 Hz, CHO). The acetate was 99% pure by GLC (Golay R, 145 °C), although with this column the epimeric exo acetate had the same retention time and would not be resolved.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 8.88.

Tetracyclo[4.3.0.$0^{2,9}$.$0^{4,8}$]nonan-3-one (29). *endo*-5-Norbornene-2-carboxylic acid (**28a**; 69 g, mp 44–44.5 °C), obtained pure from a mixture of endo and exo epimers by Berson's method,[33] was converted to its sodium salt by treatment with a solution of sodium bicarbonate (46 g), and the residue was dried at 75 °C (0.5 mm) for 24

h. The dry sodium salt (79.5 g) suspended in dry ether (500 mL) at 0 °C was added dropwise (30 min) to a stirred solution of oxalyl chloride (67 g) in anhydrous ether (150 mL). After an additional 30 min, the mixture was filtered, the filtrate was evaporated in vacuo, and two successive portions of dry benzene (30-mL each) were added and each evaporated in vacuo. The oily acid chloride (**28b**; 64 g) had IR ν (neat) 1801 (s, C=O) and 701 (s, C=C deformation).

The acid chloride (62 g) in dry ether (250 mL) was gradually added (30 min) to a stirred solution of ethereal diazomethane[34] at 0 °C. After an additional 30 min at 0 °C, evaporation in vacuo left the diazomethyl ketone **28c** as an oil (61.2 g): IR ν (neat) 3062 (m, olefinic CH), 2105 (s, diazo), 1633 (s, C=O), 708 (s, C=C deformation).

A suspension of the diazo ketone (61.2 g), copper–bronze powder (12 g), and dry tetrahydrofuran (2 L, distilled from sodium) was refluxed 50 h. The cooled mixture was filtered, the solvent was removed in vacuo, and the residue (36 g) was triturated with 600 mL of ether. Precipitated solid was removed, the ether was evaporated in vacuo, and the residue (33 g) in pentane was chromatographed on Woelm alumina (900 g, neutral, Grade II). Elution with pentane through pentane–ether (3:1) gave preliminary impure fractions (total 16 g) followed by pure fractions (total 12.2 g) monitored by GLC. Sublimation [62–66 °C (0.5 mm)] of the combined pure fractions gave white, tetracyclic ketone **29** (11.4 g), mp 90.5–92.5 °C, which showed only one peak on GLC (Golay R, 146 °C), and a molecular ion at *m/e* 134: IR ν (CCl_4) 3048 (m, cyclopropyl CH), 1734 (s, C=O), 1303 (s), 1279 (m), 903 (s), 872 cm^{-1} (s); ^1H NMR (CCl_4) δ 3.00–2.38 (m, 4), 2.38–1.40 (m, 6). UV λ_{max} (95% ethanol) 271 nm (ϵ 50); (isooctane) 278 nm (ϵ 66).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.60; H, 7.39.

Rechromatography of the impure fractions (16 g) and sublimation led ultimately to an additional 9.7 g of pure (mp 90–92 °C) tetracyclic ketone. The total overall yield of **29** from endo acid was 31%.

The **semicarbazone (29a)** of tetracyclic ketone was prepared with semicarbazide acetate in methanol conventionally (overnight in the refrigerator). A few drops of water were added, and after 15 h at room temperature the solid (mp 203.5–204 °C) was collected. Two recrystallizations from methanol for analysis gave **29a** with mp 204–205 °C: IR ν (KBr) 3445 (NH), 2060 (cyclopropyl CH), 1680 (C=O), 1590 cm^{-1} (C=N).

Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85. Found: C, 63.01; H, 6.73.

The **2,4-dinitrophenylhydrazone (29b)** was obtained by treatment of ketone **29** (overnight in the refrigerator) in 95% ethanol with 1.0 equiv of reagent and 5 drops of concentrated hydrochloric acid. The precipitate was recrystallized four times from methanol: mp 210–211 °C; IR ν (KBr) 3305 (NH), 3105 (aromatic CH), 3035 (cyclopropyl CH); UV λ_{max} (95% ethanol) 372 (ϵ 23 400), 280 sh (ϵ 7800), 271 sh (ϵ 10 200), 234 nm (ϵ 18 020).

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49. Found: C, 57.09; H, 4.46.

Attempted Preparation of *p*-Toluenesulfonylhydrazone. A solution of tetracyclic ketone **29** (0.13 g) and *p*-toluenesulfonylhydrazine (0.19 g, 1.0 equiv) in 95% ethanol (1.5 mL) containing 5% hydrochloric acid (5 drops) stood overnight at room temperature. The derived solid (probable structure **30**) was crystallized from methanol: 0.11 g; mp 164.5–165.5 °C. The analytical sample (mp 165–165.5 °C) had strong IR bands (KBr) at 3400 and 3200 (NH), but otherwise was difficult to interpret.

Anal. Calcd for $C_{23}H_{28}N_4O_4S_2$: C, 56.54; H, 5.78. Found: C, 56.88; H, 5.71.

This product was extracted from ether by 5% hydrochloric acid and was released from the acid solution with sodium bicarbonate solution. For comparison we showed that camphenilone tosylhydrazone[35] was not extracted by dilute hydrochloric acid. We did not further explore product **30**, but presume its yield would increase markedly by use of 2 equiv of reagent.

Tricyclo[4.2.1.$0^{3,7}$]nonan-4-one (Brendan-4-one) (31). A. By Catalytic Hydrogenation. A stirred solution of tetracyclic ketone **29** (5.15 g) in ethyl acetate (7 mL) was hydrogenated with 10% Pd/C (0.51 g) at 22.5 °C (744 mm) until hydrogen absorption ceased (22 h; 107% of theoretical). The filtrate in pentane (40 mL) was repeatedly washed with water and dried ($MgSO_4$). Evaporation in vacuo left a white solid (4.62 g, 89%), mp 114–116.5 °C. Hydrogenation in ether gave comparable results (86%), mp 113–118 °C. Sublimation [65–70 °C (12 mm)] gave mp 116.5–118.5 °C. The analytical sample of brendan-4-one, mp 120–120.5 °C, was obtained by regeneration from the semicarbazone (see below): IR ν (CCl_4) 1744 (s, C=O), 1703 (w), 1448 (CH_2 scissor), 1407 (m, CH_2CO scissor); ^1H NMR (CCl_4) δ 2.90–2.02 (m, 8), 2.00–1.53 (m, 3), 1.45 (s, 1), 1.25 (s, 1), 1.03 (s, 1), 0.83 (s, 1); GLC (Golay R, 148 °C) showed only one peak; molecular ion at *m/e* 136.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.63; H, 8.90.

The **semicarbazone 31a** was obtained from crude brendan-4-one (2.0 g, mp 114–116.5 °C) and semicarbazide acetate–methanol reagent (20 min on steam bath, then overnight at room temperature). The precipitate (2.9 g, mp 195–197 °C) was recrystallized from methanol for analysis: mp 195–196 °C; IR ν (KBr) 1691 (s, C=O), 1596 (m, C=N).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82. Found: C, 62.20; H, 7.85.

A stirred suspension of semicarbazone (0.75 g), oxalic acid dihydrate (1.5 g), and water (15 mL) was distilled until the distillate became clear. Pentane extraction of the distillate gave, on workup, brendan-4-one, mp (after one sublimation) 120–120.5 °C (~45% yield).

B. By Li/NH_3 Reduction. A solution of tetracyclic ketone (2.5 g) in anhydrous ether (75 mL) was rapidly added to a solution of freshly cut lithium (1.30 g) in liquid ammonia (150 mL) in a flask equipped with an overhead stirrer and a dry ice–acetone cooled condenser. The solution was stirred and allowed to reflux 4 h. Solid ammonium chloride (5.0 g) was added, the mixture was stirred an additional 10 min, and the condenser was removed to allow the ammonia to evaporate from the stirred mixture. Conventional water–pentane workup left a semisolid (1.78 g), whose GLC (Golay R, 145 °C) revealed brendan-4-one (86%), three unknowns (total 4%), and starting ketone (10%) in that order of elution. The crude product was shaken for 3.5 h with 40% aqueous sodium bisulfite (15 mL). The derived white precipitate (1.86 g) was collected and stirred 15 h in a solution of sodium carbonate (3 g) in water (15 mL). Conventional pentane workup gave pure brendan-4-one (0.63 g, mp 116–117.5 °C) identical in infrared absorption with that of the analytical sample prepared above.

Deuterium Exchange in Brendan-4-one (31). A solution of brendan-4-one (0.10 g, mp 119–120 °C), D_2O (0.5 mL), methanol-*O*-*d* (2 mL), and potassium carbonate (0.10 g) was refluxed 7 days in a drybox. The solution was extracted with purified petroleum ether (bp 35–40 °C), which was then washed with D_2O, dried ($MgSO_4$), and evaporated in vacuo. Two sublimations of the solid residue [bath 60–80 °C (15 mm)] gave: mp 118.5–119.5 °C; one peak on GLC (Golay R, 137 °C); IR ν (CCl_4) 2215 (w) and 2132 (w, CD), 1738 (s, C=O), 1189 (s), 1160 (m), 1129 (m), 1076 (m), 1019 cm^{-1} (s). The characteristic CH_2CO "scissor" band at 1407 cm^{-1} was absent. Mass spectral assay showed 99.5% d_2; 0.5% d_1; 0% d_0.

Baeyer–Villiger Oxidation of Brendan-4-one (31). A solution of trifluoroperoxyacetic acid[28] prepared from trifluoroacetic anhydride (5.08 mL), methylene chloride (10 mL), and 98% hydrogen peroxide (0.85 mL) was added during 10 min to a cold (0 °C) stirred solution of brendan-4-one (2.72 g, mp 118–120 °C), disodium hydrogen phosphate (13.0 g), and methylene chloride (30 mL). After an additional 15 min at 0 °C, 30 min at room temperature, and 30 min at gentle reflux, the mixture was filtered. The methylene chloride was washed with saturated sodium bicarbonate and then brine, dried ($MgSO_4$), and evaporated in vacuo to leave a semisolid mixture of lactones **32** and **33** (2.71 g), IR ν (neat) 1739 cm^{-1}. (This material could be crystallized from pentane at 0 °C, but the derived solid, mp 102–104 °C, showed an IR spectrum little changed from that of the semisolid.)

The semisolid lactone mixture (2.71 g), sodium hydroxide (1.0 g), and water (25 mL) were shaken on the steam bath for 45 min. The cooled alkaline solution was washed with ether, saturated with solid sodium chloride, and, at 0 °C, acidified with 10% hydrochloric acid, followed by rapid extraction with ether (5 × 15 mL). Each ether extract was immediately poured into an ethereal solution of diazomethane, which was then reduced in volume to ~30 mL, dried ($MgSO_4$), and evaporated in vacuo. The residual oil (2.61 g) had: IR ν (neat) 3442 (m, br, OH), 1741 (s, sh on low frequency side, C=O, methyl ester and δ-lactone).

This mixture (2.60 g) of hydroxymethyl ester and δ-lactone (**33**) in ether (9 mL) was oxidized with Brown's reagent (15 mL)[20] for 12 h at 0 °C. The layers were separated, and normal workup of the ether layer left 1.97 g: IR ν (neat) 1740 (s, sh on high frequency side, C=O; ester, lactone, cyclopentanone); GLC (Golay Castorwax, 132 °C) showed the keto ester **35a** (eluted first) and the δ-lactone **33** in the ratio 1:1.2.

This mixture (1.90 g) of keto ester and δ-lactone was stirred and heated on the steam bath for 1 h with sodium hydroxide (0.65 g) and water (20 mL). The cooled, clear solution was washed with ether (3 × 5 mL) and acidified with 20% hydrochloric acid. After 5 min the acid mixture was made alkaline with solid sodium carbonate, and the lactone **33** was extracted with ether (4 × 4 mL).

The alkaline layer was acidified with 20% hydrochloric acid and the keto acid **35b** was extracted with ether (4 × 4 mL), and the acid solution was then reextracted continuously for 24 h with ether (10 mL). Workup of the combined ether extracts left keto acid **35b** as an oily solid (0.62 g), which was washed with petroleum ether and crystallized to constant melting point from benzene–petroleum ether: 0.51 g; mp 98.5–99 °C; IR ν (KBr) 1703 (s, acid C=O), 1738 (s, C=O cyclopentanone), 1425 (s), 1306 (s), 1296 (s), 1251 (s), 1224 (s), 926 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.95–1.66 (m, 11), 1.25–0.83 (m, 1).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.53; H, 7.19.

Treatment of keto acid **35b** with ethereal diazomethane gave the colorless, liquid methyl ester **35a** after one distillation [bath 110–115 °C (0.4 mm)], $n^{23}D$ 1.4757. Its IR and ^1H NMR spectra were superposable on those of an authentic sample prepared from **34a** by an Arndt-Eistert sequence described below.

The ether extracts from above, containing the lactone **33**, were washed with water, dried ($MgSO_4$), and evaporated in vacuo. The solid δ-lactone **33** (0.61 g) was repeatedly recrystallized at 0 °C from minimum amounts of pentane: 0.31 g; mp 125–126.5 °C; GLC (Golay Castorwax, 129 °C) indicated >99.5% purity; IR ν (KBr) 1738 (s, C=O), 1240 (s), 1221 (s), 1143 (s), 1078 (s), 1053 (s), 1002 cm^{-1} (s); ^1H NMR (CCl_4) δ 4.42 (s, 2, CH_2O), 2.66–1.08 (m, 10).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.99; H, 8.01.

Synthesis of Keto Ester 35a by Arndt–Eistert Homologation of Keto Acid 34. Purified thionyl chloride (5.4 g) in dry ether (50 mL) was added during 20 min to a stirred, cold (0 °C) solution of 6-oxobicyclo[2.2.1]heptane-*endo*-2-carboxylic acid (**34a**, 7.0 g, mp 102–103 °C, prepared as reported[17]) and dry pyridine (3.7 g) in dry ether (240 mL). After 1.5 h the mixture was rapidly filtered through sintered glass, and the ether was evaporated in vacuo. Traces of thionyl chloride were removed by two successive additions of dry benzene (15 mL) and evaporation. The residual oily acid chloride **34b** (6.9 g) had: IR ν (neat) 1802 (s, C=O of acid chloride), 1747 (s, C=O cyclopentanone), 1410 (m), 1000 cm^{-1} (s).

The acid chloride (6.9 g) in dry ether (50 mL) was added during 5 min to a cold (0 °C) stirred solution of diazomethane (~3.9 g) in ether (~250 mL).[34] About 15 min after vigorous N_2 evolution had ceased, the solvent was evaporated in vacuo, the oily residue was dissolved in dry benzene (~20 mL), and hexane was added until the solution became cloudy. After 3 h in a freezer (−20 °C) the clear supernatant solution was decanted from some oil that had formed and was kept in the freezer overnight. Pale yellow crystals of the diazomethyl ketone **34c** precipitated: 4.5 g; mp 66–73 °C; IR ν (CCl_4) 3106 (m, CH), 2114 (s, diazo), 1751 (s, C=O cyclopentanone), 1653 (s, C=O diazomethyl ketone), 1409 (m), 1310 (m), 1043 cm^{-1} (s).

A clear solution (2.8 g) of silver benzoate in triethylamine (made from 1.0 g of silver benzoate in 9.0 g of triethylamine) was added dropwise during 30 min to a stirred solution of the diazomethyl ketone **34c** (4.4 g) in methanol (50 mL). After an additional 30 min, the mixture was heated on the steam bath for 10 min, the solvent was evaporated in vacuo, and the residue was taken up in ether (75 mL), which was washed successively with 5% sulfuric acid, 5% sodium bicarbonate, and water, and dried ($MgSO_4$). The liquid keto ester (2.8 g), which contained about 5% of an impurity as revealed by GLC (Golay R, 146 °C), was chromatographed on alumina (85 g, which we prepared by shaking 100 g of Woelm alumina, neutral, Grade I with 3 g of water for 1 h). Graded elution with pentane up to pentane–ether (15:1) gave 1.83 g of homogeneous product, as judged by GLC (Golay Castorwax 100 °C). Two bulb-to-bulb distillations [bath 110–115 °C (0.5 mm)] gave the colorless, liquid keto ester **35a** (1.5 g), 99.5% pure by GLC (Golay R, 146 °C): $n^{23}D$ 1.4757; IR ν (neat) 1740 (s, br, C=O of ester and ketone), 1454 (m), 1438 (s), 1411 (m), 1374 (m), 1291 (s), 1205 (s), 1169 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.71 (s, 3, OCH_3), 2.83–0.83 (m, 11).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.22; H, 7.78.

2′-(2-Hydroxy-*endo*-6-bicyclo[2.2.1]heptyl)ethanol (36). The keto ester **35a** (0.40 g) in dry ether (10 mL) was added during 5 min to a cold (0 °C), stirred suspension of $LiAlH_4$ (0.30 g) in dry ether (50 mL). After 2 h at 0 °C more $LiAlH_4$ (0.10 g) was added, and stirring was continued 10 h at room temperature. After water (3 mL) was carefully added, followed by 10% aqueous sulfuric acid (30 mL), the mixture was stirred 30 min, and the ether layer was separated, washed with 5% sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The diol **36** (0.31 g) was crystallized once from benzene–pentane: 0.25 g; mp 67.5–70 °C. It was sublimed once [bath 110–115 °C (0.5 mm), 0.21 g, mp 70.5–73 °C] and recrystallized for analysis: 0.20 g; mp 73–74.5 °C; IR ν (KBr) 3350 (OH), 1128 (m), 1071 (m), 1044 (s), 989 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 4.62–3.58 (m, 6), 2.57–1.66 (m, 6), 1.45–0.78 (m, 4). On addition of D_2O a peak at δ 4.15 disappeared.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.51; H, 10.21.

Haller–Bauer Cleavage of Brexan-2-one (10). A stirred suspension of brexan-2-one (0.08 g), sodium amide (0.40 g), and diisopropyl ether (5 mL; distilled from $LiAlH_4$) was refluxed 8 h. Water (1 mL) was carefully added to decompose the excess of reagent, and the mixture was worked up with water and ether. The ether layer was washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and brine, and dried ($MgSO_4$). Evaporation left a crude solid (0.047 g, mp 157–161 °C), which was recrystallized from hot water and finally from benzene–pentane, mp 161–161.5 °C undepressed on admixture with an authentic sample[12] (mp 161 °C) of *cis*-bicyclo[3.3.0]octane-*cis*-2-carboxamide (**38**). The infrared spectra (KBr) were also identical.

Haller–Bauer Cleavage of Brendan-2-one (25). A suspension of brendan-2-one (0.16 g), sodium amide (0.60 g), and dry diisopropyl ether (10 mL) was refluxed 9 h. When cool, the liquid phase was decanted, water was carefully added to the residual sodium amide, and the resulting aqueous solution was extracted with chloroform. The isopropyl ether solution was evaporated in vacuo, water was added, and the mixture was extracted with chloroform. The chloroform extracts were combined, washed with water, dried ($MgSO_4$), and evaporated in vacuo: 0.13 g (74%); mp 115–130 °C; IR ν ($CHCl_3$) 3484 (m, free NH), 3379 (m, bonded NH), 1678 (s, $CONH_2$). Gas chromatography (Golay Z, 200 °C) showed two peaks in the ratio 1:13. Recrystallization from hot CCl_4 and then from benzene–pentane gave a constant mp 136–137 °C (0.050 g). Chromatography of the mother liquors on alumina (Woelm neutral, Grade I) gave a second crop (0.031 g): mp 136.5–138.5 °C (from ether); IR ν (KBr) 3379 (s) and 3193 (s, NH), 1657 (s) and 1628 (s, $CONH_2$), 1423 (m), 1291 (m), 1127 cm^{-1} (m). The reported melting point for *cis*-bicyclo[3.3.0]octane-*trans*-3-carboxamide (**39**) is 135–136 °C, and that for the C-3 epimer is 153 °C.[13]

Tricyclo[4.2.1.$0^{3,7}$]nonane (Brendane) (40). A. By Wolff–Kishner Reduction of Brendan-4-one (31). A solution of brendan-4-one (0.55 g, mp 118–120 °C) and 95% hydrazine (2.5 mL) in diethylene glycol (7 mL) was heated slowly from 25 to 135 °C during 1 h, while nitrogen gas was bubbled through gently. Around 135 °C distillate started to collect, and distillation was continued until the temperature reached 220 °C. When cool, the solution of hydrazone was treated with a clear solution of freshly cut sodium (0.20 g) in deoxygenated diethylene glycol (3 mL). While being purged with a nitrogen stream, the solution was heated, and at 180 °C gas was evolved and a white, waxy solid began to sublime into the collector. After continued heating at 200–215 °C for 4 h the collected sublimed solid in CS_2 (10 mL) was successively washed with water, 5% hydrochloric acid, and brine, and dried ($MgSO_4$). GLC (5% squalane on Chromosorb, 135 °C) at this stage showed 98% of one component. Preparative GLC with the same column gave 0.093 g: IR ν (CS_2) 1310 (m), 1287 (m), 1252 (w), 1148 cm^{-1} (m); IR ν (CCl_4) 1453 (m), 1311 (m), 1288 (m), 1251 (w), 1149 cm^{-1} (m); ^1H NMR (CCl_4) δ 2.33–1.38 (m), 0.87 (s), 0.70 (s). Because of overlap, accurate relative intensities were not obtained. Sublimation for analysis [bath 80–90 °C (760 mm)] gave white brendane (**40**): mp 98–99 °C (N_2 filled, sealed tube); molecular ion at *m/e* 122.[36]

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.20; H, 11.54.

B. By Wolff–Kishner Reduction of Brendan-2-one (25). The reduction of brendan-2-one (0.40 g, mp 118.5–119.5 °C) was conducted as described for brendan-4-one with proportional amounts of reagents. Preparative GLC of the CS_2 solution gave 0.053 g of brendane, whose IR in CS_2 and NMR in CCl_4 were superposable on those of the hydrocarbon from part A. After sublimation, it had mp 98.5–99 °C (N_2 filled, sealed tube) with softening at 70 °C. A mixture melting point with brendane from part A had mp 98–99 °C.

Tricyclo[4.3.0.$0^{3,7}$]nonane (Brexane) (37). A. By Wolff–Kishner Reduction of Brexan-2-one Semicarbazone (10a). A mixture of brexan-2-one semicarbazone (0.43 g, mp 188–189.5 °C) and powdered potassium hydroxide (0.57 g) in a bulb-to-bulb distillation apparatus was slowly heated in an oil bath while the receiver bulb was cooled in dry ice. At 180 °C gas evolution began and heating was continued at 185–200 °C for 2 h. The distillate was dissolved in CS_2, which was successively washed with water, 5% hydrochloric acid, 5% sodium bicarbonate, and water, and dried ($MgSO_4$). Purification by preparative GLC (Carbowax on Chromosorb W, 147 °C) gave 0.11 g of liquid, which was dried with $MgSO_4$ and distilled [bath 120–150 °C (760 mm)] from $LiAlH_4$ to give colorless brexane (**37**) (0.072 g): one peak on GLC (squalane, 132 °C); $n^{25}D$ 1.4845; IR ν (CCl_4) 1462 (m), 1307 (m); ^1H NMR (CCl_4) 2.05–1.73 (m, 4), 1.73–0.92 (m, 10); molecular ion at *m/e* 122.

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.55; H, 11.50

B. By Wolff–Kishner Reduction of Brexan-4-one Semicarbazone (24a). Brexan-4-one semicarbazone (0.35 g, mp 202–204 °C) was reduced with powdered potassium hydroxide (0.45 g) in a manner essentially the same as that described above in part A. After preparative GLC the colorless product (0.063 g) had n^{25}_D 1.4843 and its IR in CCl_4, its retention time on GLC (squalane, 132 °C), and its mass spectral cracking pattern were identical with those of brexane obtained by method A.

Brexan-2-one *p*-Tosylhydrazone (10b). A solution of brexan-2-one (0.050 g) and *p*-toluenesulfonylhydrazine (0.075 g, mp 110–111 °C) in methanol (1 mL) was refluxed 30 h. Removal of the solvent in vacuo left a white solid (0.093 g, mp 140–143 °C), which was recrystallized from methanol–water for analysis: 0.068 g; mp 148–149.5 °C; IR ν (KBr) 3200 (s), 1671 (m), 1600 (m), 1344 (s), 1162 (s), 815 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 63.39; H, 6.71.

Brendan-2-one *p*-Tosylhydrazone (25b). A solution of brendan-2-one (0.013 g) and *p*-toluenesulfonylhydrazine (0.038 g) in absolute methanol (1 mL) was heated gently on a steam bath for 30 min. Water (1 mL) was added and the solution was heated briefly and allowed to cool. The first crop of crystals (~70%) was recrystallized twice from methanol–water (1:1), mp 146.5–147.5 °C.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 63.30; H, 6.66.

Brexan-4-one *p*-Tosylhydrazone (24b). This derivative was prepared from brexan-4-one in the same manner as used for brendan-2-one. Recrystallization from absolute methanol gave mp 192.5–193.5 °C dec.

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62. Found: C, 62.76; H, 6.52.

Bamford–Stevens Reaction on Brexan-2-one Tosylhydrazone (10b). A stirred mixture of brexan-2-one tosylhydrazone (0.685 g, mp 146–148 °C), sodium methoxide (0.833 g, freshly prepared and thoroughly dried), and bis(2-ethoxyethyl) ether [4.5 mL, dried repeatedly over KOH and distilled, bp 78–79 °C (15 mm)] was heated on an oil bath. At 140 °C (bath temperature) nitrogen was vigorously evolved. After 2 h at 140–150 °C, water was added to the cooled solution, which was then extracted with pentane. The extract was washed with water and dried over $MgSO_4$, and the solvent was removed on an 18-in. spinning-band column (reflux ratio 5:1) until the boiling point reached 60 °C. The residual pot solution was preparatively gas chromatographed (20% SE-30 on Chromosorb P, 132 °C). The colorless liquid (0.142 g) had n^{23}_D 1.4921, showed only one GLC peak (Golay R, 118 °C), and its IR (neat) and ^1H NMR (CCl_4) were superposable on those of authentic deltacyclane (21).

Bamford–Stevens Reaction on Brexan-4-one Tosylhydrazone (24b). A stirred mixture of the tosylhydrazone (0.161 g, mp 192–192.5 °C), dry sodium methoxide (0.15 g), and purified bis(2-ethoxyethyl) ether (2.5 mL) was heated on an oil bath. Gas was evolved around 155 °C and heating was continued for 1.5 h at 155–160 °C. After a water–pentane workup, the dried pentane layer gave 0.024 g of liquid after preparative GLC (20% SE-30 on Chromosorb P, 130 °C), n^{25}_D 1.4928. It showed only one peak on GLC (squalane, 132 °C), and its IR (CCl_4) and mass cracking pattern were identical with those of authentic deltacyclane (21).

Bamford–Stevens Reaction on Brendan-2-one Tosylhydrazone (25b). This reaction was conducted on 0.304 g of brendan-2-one tosylhydrazone (mp 140–144 °C) as described above for the brexan-4-one analogue, with proportional quantities of reagents. After preparative GLC the product (0.049 g; n^{25}_D 1.4928) showed only one peak on GLC (squalane, 132 °C) and had an IR (neat) that was identical with that of authentic deltacyclane (21).

Brexane (37) from Catalytic Hydrogenation of Deltacyclane (21). The tetracyclic hydrocarbon 21 (0.12 g), platinum oxide (0.040 g), and acetic acid (10 mL) were hydrogenated at 95 °C and 100 psi for 4.5 h. After conventional workup, GLC on squalane showed deltacyclane and brexane in the ratio of 2:1. (Possibly a small proportion of brendane may have escaped detection in the tailing peak.) *exo*-2-Brendyl acetate and *exo*-4-brexyl acetate were not detected with the squalane column, but were principal products, as revealed by use of appropriate columns (polypropylene coated Golay).

Isomerization of Brexan-2-one (10) to Brendan-2-one (25) by Alkali. A solution of brexan-2-one (0.20) and potassium *tert*-butoxide [0.51 g, M.S.A. Corp., sublimed twice at 135–140 °C (0.3 mm)] in *tert*-butyl alcohol (5.7 mL, twice distilled under nitrogen from sodium) was heated in a sealed Pyrex tube for 150 h at 185 °C in a bomb with external *tert*-butyl alcohol as a pressure equalizer. Water (15 mL) was added, and the mixture was extracted with pentane (5 × 4 mL), which was then washed with water and brine, dried with $MgSO_4$, and concentrated to ~4 mL with an 18-in. spinning-band distillation column. The remaining solvent was removed in vacuo and the residue was sublimed [bath 60–80 °C (13 mm)] to give a white solid (0.12 g, 57%), mp 117.5–118.5 °C undepressed by an authentic sample of brendan-2-one. Their IR spectra (CCl_4) were also identical. GLC (Golay R, 124 °C) showed >99% brendan-2-one and <1% brexan-2-one.

In a control homoenolization experiment conducted similarly (185 °C for 120 h) on **brendan-2-one,** the product (~100%) was brendan-2-one, which contained (GLC on Golay Castorwax, 110 °C) ~4% of an unidentified compound, which was not brexan-2-one. A second control run on brendan-2-one for 60 h at 205 °C and similar workup again gave no brexan-2-one, but led to extensive decomposition. The crude product (~35% yield by weight) showed five peaks on GLC (Golay Castorwax, 100 °C) in the ratio 2:2:1:4:10. The first peak corresponds to brendan-2-one.

Acknowledgments. This paper is dedicated to the memory of our co-worker, the late T. D. Swartz. His enthusiasm, keen perception, laboratory skill, and high spirit played crucial roles in this project. The research was supported by Grants from the National Science Foundation and the National Institutes of Health. A predoctoral N.I.H. fellowship (to T.S.) and an Esso Foundation fellowship (to H.K.) are gratefully acknowledged.

Registry No.—**6a,** 57722-41-5; **6a** sodium salt, 57722-42-6; **6b,** 57722-43-7; **6c,** 1703-68-0; **7,** 1703-69-1; *exo*-**8a,** 66840-95-7; *endo*-**8a,** 66840-96-8; *exo*-**8b,** 66840-97-9; *endo*-**8b,** 66840-98-0; **9,** 1703-77-1; **10,** 1703-78-2; **10a,** 1703-79-3; **10b,** 66787-57-3; **11,** 1521-91-1; **11a,** 66787-64-2; **11b,** 66787-65-3; **11c,** 66787-66-4; **12,** 121-46-0; **13** epimer 1, 66808-07-9; **13** epimer 2, 66808-08-0; **14a** epimer 1, 29415-45-0; **14a** epimer 2, 66808-09-1; **14b** epimer 1, 13927-45-2; **14b** epimer 2, 13927-44-1; **14c,** 66787-58-4; **15,** 66787-59-5; **16,** 66787-60-8; **17a,** 1007-04-1; **17b,** 29412-43-9; **17c,** 21519-81-3; **18,** 66787-61-9; **19,** 16282-07-8; **19a,** 66787-62-0; **19b,** 66787-63-1; **20a,** 939-84-4; **20b,** 21519-84-6; **20c,** 21519-85-7; **21,** 6567-11-9; **22a,** 61800-16-6; **22b,** 61800-18-8; **22c,** 61800-17-7; **23a,** 61800-14-4; **23b,** 14805-44-8; **23c,** 61800-15-5; **23d,** 66787-54-0; **24,** 53439-20-6; **24a,** 66787-55-1; **24b,** 66787-56-2; **25,** 1521-92-2; **25a,** 1521-93-3; **25b,** 1521-73-9; **26a,** 66808-03-5; **26b,** 66808-04-6; **27a,** 66808-05-7; **27b,** 66808-06-8; **28a,** 1195-12-6; **28a** sodium salt, 66787-51-7; **28b,** 37750-50-8; **28c,** 35964-13-7; **29,** 1719-13-7; **29a,** 1719-09-1; **29b,** 1521-79-5; **30,** 66787-52-8; **31,** 1521-78-4; **31a,** 1521-77-3; **32,** 26433-43-2; **33,** 66787-53-9; **34a.** 42392-37-0; **34b,** 66787-45-9; **34c,** 66787-46-0; **35a,** 1719-08-0; **35b,** 1521-76-2; **36,** 66787-47-1; **37,** 3104-87-8; **38,** 66787-50-6; **39,** 7067-97-2; **40,** 1521-75-1; *exo*-2-bicyclo[2.2.1]hept-5-enecarboxylic acid, 934-30-5; *endo*-2-bicyclo[2.2.1]hept-5-enecarboxylic acid, 1195-12-6; *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylic acid, 66808-01-3; methyl *exo*-2-hydroxy-*syn*-7-bicyclo[2.2.1]heptanecarboxylate, 66787-49-3; methyl *syn*-2-oxo-7-bicyclo[2.2.1]heptane carboxylate, 66808-02-4; α-naphthyl isocyanate, 86-84-0; 3,5-dinitrobenzoyl chloride, 99-33-2; methyl vinyl ketone, 78-94-4; α-acetoxyacrylonitrile, 3061-65-2; methyl 6-hydroxy-2-bicyclo[2.2.1]-heptaneacetate, 66787-48-2.

References and Notes

(1) (a) A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87**, 1613 (1965); (b) presented at the 149th Meeting of the American Chemical Society, Detroit, Michigan, April, 1965, Abstracts 2P.

(2) The parent hydrocarbon **1** (Z = H) is tricyclo[4.3.0.$0^{3,7}$]nonane, and can be viewed as a norbornyl system with an extra two-carbon bridge that uses an *exo*-norbornyl bond. The convenient trivial name *brexane* derives from the words *bridge* and *exo*.

(3) For a recent review, see: H. C. Brown, "The Nonclassical Ion Problem", Plenum Press, New York, N.Y., 1977.

(4) The parent hydrocarbon **5** (Z = H) is tricyclo[4.2.1.$0^{3,7}$]nonane. A convenient name for the skeleton is *brendane*, which emphasizes the existence of a *bridge* involving an *endo*-norbornyl bond.

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(6) Several research groups have contacted us for comparison samples, spectral data, experimental procedures, and mechanistic or other details about various brexyl, brendyl, and related derivatives. We wish to acknowledge mutually beneficial correspondence from J. H. Richards (California Inst tute of Technology); R. S. Bly (University of South Carolina); R. M. Moriarty (University of Illinois, Chicago Circle); W. R. Adams, D. Heywood, and E. Marcus (Union Carbide Corp., South Charleston, W. Va.); M. Julia (University of Paris); A. Krantz (State University of New York, Stony-

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(7) The fourth letter of the Greek alphabet led to the convenient name *deltacyclane* for this key tetracyclic hydrocarbon, whose full IUPAC name is given in the Experimental Section. We avoided prefixes like *quad* or *tetra* to prevent confusion with the tetracyclic hydrocarbon, quadricyclane, and with the "tetracycline" class of antibiotics.

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Marine Natural Products: Halitoxin, Toxic Complex of Several Marine Sponges of the Genus *Haliclona*[1]

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A complex mixture of high molecular weight toxic pyridinium salts designated halitoxin has been isolated from the sponges *Haliclona rubens*, *H. viridis*, and *H. erina*. The toxin has been separated into molecular weight range fractions of 500–1000, 1000–25 000, and > 25 000, each of which shows the same spectral and biological properties. A general structure for halitoxin has been proposed based on ^{1}H and ^{13}C NMR analyses and identification of a group of 3-alkenylpyridines obtained in good yield upon pyrolysis of the toxin. The oligomeric/polymeric toxin consists of 3-alkylpyridine units connected by the nitrogen of one ring and the terminus of the 3-alkyl chain of the next. No functionality other than the pyridinium ring has been detected. Halitoxin is cytotoxic, haemolytic, and toxic to fish and mice.

Sponges from several species of the genus *Haliclona* have been reported to give extracts toxic to fish.[2] Baslow and Turlapaty[3] found that a crude aqueous extract of *H. viridis* was toxic to mice (LD_{50} ~ 275 mg/kg) and also inhibited the growth of Ehrlich ascites tumors. These authors coined the name halitoxin for this crude toxic extract but did not report any effort to isolate a pure toxin. In our ongoing search[4] for pharmacologically active compounds from marine organisms, we found that extracts of *H. rubens* are toxic to mice (LD_{50} ~ 7 mg/kg) and fish and cytotoxic in the National Cancer Institute's KB cell culture bioassay.[5] We also have found that other species of the genus *Haliclona* contain what appears to be the same toxin. However, not all of the *Haliclona* sp. examined yielded the toxin. In this paper we report the partial purification, spectral characterization, and chemical degradation which have lead to a proposed gross structure for halitoxin from four different *Haliclona* species.

The sponge we have studied most extensively is *Haliclona rubens*, a red tubular sponge commonly found in shallow (15 ft or less) reef waters of the Caribbean. Samples of the sponge for chemical work have been preserved in various ways: air-dried, freeze-dried shortly after collection, and preserved in alcohol. The method of preservation appears to have little effect on the character of the toxin isolated as judged by biological activity and spectral analysis. The toxin is obtained easily from the sponge preserved by any of the above methods.

Isolation and Purification of Halitoxin. Toxin was obtained from air-dried *H. rubens* by first defatting the ground specimens with chloroform and then extracting them continuously with methanol. After removal of most of the solvent, the methanol extract was dissolved in water and extracted several times with 1-butanol. The 1-butanol fractions contained virtually all of the toxin as determined by spectral

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analysis and bioassay.

Halitoxin was obtained from freeze-dried and alcohol-preserved specimens using a slightly different extraction sequence. Freeze-dried sponges were extracted with methanol continuously to give a crude extract. In the case of alcohol-preserved sponges, the crude extract was obtained by filtration and evaporation of the solvent. The alcohol extracts, diluted with water, were defatted by extraction with dichloromethane and then extracted several times with 1-butanol. The butanol fraction contained the toxin.

Further purification of the crude toxin has been accomplished most effectively and efficiently by membrane ultrafiltration of aqueous solutions. Low molecular weight materials were removed by the use of a 500 nominal molecular weight cutoff membrane. The <500 molecular weight materials were neither cytotoxic nor toxic to mice, and they did not show any of the spectral characteristics observed for the toxic fractions. The retentate was divided into molecular weight range fractions of 500–1000, 1000–25 000, and greater than 25 000 by successive ultrafiltrations using membranes with a larger pore size at each step. After lyophilization, these fractions were obtained as hygroscopic brown foams or glasses. The ^{1}H NMR spectra of the three different molecular weight range samples were virtually identical. The crude toxin in the 1-butanol extract, and all of the different molecular weight range fractions, exhibited the same cytotoxicity against the KB line of cancer cells (ED_{50} = 5–7 μg/mL). The LD_{50} in mice of the 1-butanol extract and of the 500–1000 molecular weight range fraction was ~5 mg/kg.

The crude toxin, a quaternary ammonium salt, also was purified via picrate formation. The picrate could not be recrystallized but was separated into acetone-soluble and -insoluble portions by repeated triturations with hot acetone. Halitoxin was recovered by dissolving the acetone-soluble picrate in an aqueous hydrochloric acid–acetone mixture and then extracting with ether to remove picric acid. This gave halitoxin in which the counterion was assumed to be exclusively chloride.

Some of the 500–1000 molecular weight range material was chromatographed on ion exchange columns in order to effect further purification and convert the toxin exclusively to the chloride form. The toxin was strongly retarded on a carboxylic acid resin and was eluted with 1 M sodium chloride. Anion exchange was also achieved by chromatography in water over the chloride form of a quaternary ammonium ion column. Comparison of the analytical data on crude, ultrafiltered, and ion exchange purified halitoxin indicated that chloride ion is the predominant, if not exclusive, counterion in the native toxin.

Of the numerous methods applied to attempt to purify halitoxin, ultrafiltration was found to be the most effective and efficient. Little additional purification was effected by chromatography subsequent to ultrafiltration. The alternate and supplementary means of purification consisted of chromatography using a variety of the common inorganic adsorbents, ion exchange resins, Sephadex gels, polypropylene powder,[6] 10% acetylated cellulose, and Carbowax-treated controlled pore glass beads.[7]

Characterization and Structure Determination of Halitoxin. Combustion analysis, spectral characterization, and chemical degradation of halitoxin have been carried out on toxin that has been purified in various ways: chromatography on silica gel, membrane filtration, ion exchange chromatography, and regeneration from the picrate complex. All of these materials exhibited virtually identical ^{1}H NMR spectra and the same degree of biological activity.

Combustion analysis of different preparations of halitoxin gave fairly consistent ratios for C, H, N, Cl and showed that small but variable amounts of phosphorus and sulfur were present. An empirical formula of $(C_{15}H_{24}NCl{\cdot}2H_2O)_n$ was reasonably consistent with the analytical data (see below) if sulfur and phosphorus are assumed to be due to impurities. That the samples contained water was corroborated by ^{1}H NMR analysis (see Figure 1). If the maximum sulfur and phosphorus values are included in the calculation, a minimum molecular weight of ~2300 is calculated. This is considerably greater than the 500–1000 molecular weight range assigned to one of the fractions on the basis of ultrafiltration behavior. While the inclusion of sulfur and/or phosphorus cannot rigorously be ruled out on the basis of the analytical data, these elements do appear to be, at the most, very minor components in halitoxin, and we believe they are due to impurities.

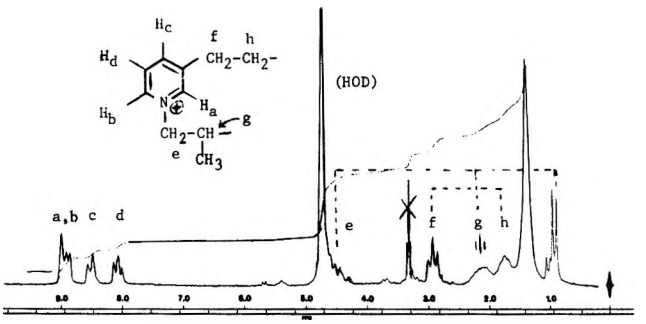


Figure 1. NMR spectrum of halitoxin (100 MHz, CD_3OD).

All of the spectral data characterized halitoxin as an alkylpyridinium salt without any other functionality. Halitoxin exhibited UV absorption characteristic[8] of an alkylpyridinium salt [λ_{max} 267 nm, 273 (sh), and 212], while the infrared spectrum showed absorption at 1640 cm^{-1}, typical[9] of such salts. The possibility that the IR absorption at 1640 cm^{-1} was due to an amide or any other type of carbonyl group was ruled out by ^{13}C NMR data; i.e., no peaks were observed below 146 ppm. Broad absorption was observed in the hydroxyl region of the infrared spectrum (centered at 3400 cm^{-1}), but this was attributed to water of hydration in the samples. The possibility that halitoxin possesses hydroxyl groups was eliminated by virtue of the fact that the toxin did not undergo acetylation or formylation under a variety of conditions and that the ^{1}H NMR and ^{13}C NMR spectra were devoid of the signals characteristic of alcohols.

The ^{1}H NMR spectrum (see Figure 1) provided convincing evidence for a 3-substituted pyridinium ring in halitoxin and also revealed many of the remaining structural features. Both the chemical shift and multiplicity of the aromatic protons, labeled a–d, match closely those of the model compounds, 1-isobutyl-3-methylpyridinium bromide (**2**) and 1-hexadecyl-3-methylpyridinium bromide (**3**) (see Experimental Section). The signal at δ 4.5, labeled e, largely obscured by the HOD peak, is attributed to the methylene group bonded to the quaternary nitrogen. Addition of a few drops of pyridine-d_5 shifted the HOD peak downfield slightly and revealed a complex multiplet at δ 4.5 corresponding to approximately two protons. Decoupling showed that these protons were coupled to the proton(s) absorbing at approximately δ 2.22 (protons g), which in turn were coupled to the methyl doublet at δ 0.92, thus demonstrating that a large percentage of the alkyl groups attached to nitrogen are methyl substituted β to nitrogen. The broad signal at δ 2.22 is resolved into two one-proton multiplets at 360 MHz (δ 2.06 and 2.22). Only one of these, δ 2.22, is coupled to both the methyl group at δ 0.92 and the methylene protons adjacent to the pyridinium nitrogen, again confirming that the predominant type of alkyl residue bonded to nitrogen is methyl branched, as indicated in Figure 1.

At 360 MHz, the protons labeled e are observed as two signals, δ 4.42 (~1 H) and 4.68 (~2 H). The δ 4.42 signal is a dd,

Table I. GC/MS Data[a] for 3-Alkenylpyridines from Halitoxin from *H. rubens*

GC fraction[b]	EI, *m/e* M^+ (%)	CI, *m/e* $(M+1)^+$ (%)	CI, *m/e* $(M+29)^+$ (%)	Formula/structure
A	189 (9)	190 (100)	218 (13)	$C_{13}H_{19}N$/4
B	203 (7)	204 (100)	232 (10)	$C_{14}H_{21}N$/8
C	203 (5)	204 (100)	232 (20)	$C_{14}H_{21}N$/5
D	217 (4)	218 (100)	246 (28)	$C_{15}H_{23}N$/6
E	231 (3)	232 (100)	260 (20)	$C_{16}H_{25}N$/9
F	231 (5)	232 (100)	260 (18)	$C_{16}H_{25}N$/7
G	243 (1)	244 (93)	272 (3)	$C_{17}H_{23}N$/10
		230 (100)	258 (13)	$C_{17}H_{21}N$/?
H	238 (2)	240 (56)	268 (12)	$C_{14}H_{22}HCl$/11
	240 (0.5)	242 (20)	270 (3)	
		204 (100)		
I	252 (0.5)	254 (60)	282 (7)	$C_{15}H_{24}NCl$/12
		256 (13)	284 (3)	
		218 (100)		
J	232 (8)	268 (100)	297 (1.5)	$C_{16}H_{28}NCl$/?
	$(M^+ - HCl)$	270 (22)	298 (1.5)	
		232 (100)		

[a] A 6 ft × 1/8 in 10% Carbowax 20M/2% KOH column; programmed at 150–230 °C (2 °C/min). [b] See Table III.

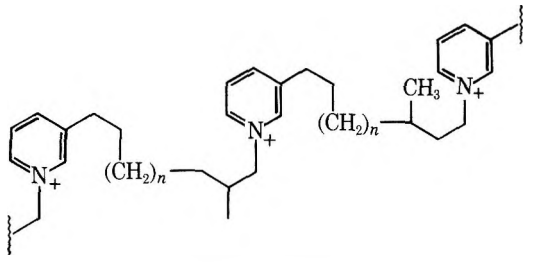
J = 8 and 13 Hz, in which the small coupling arises from interaction with the proton resonating at δ 2.22 and the large coupling is due to geminal coupling as expected for one of the diastereotopic protons at e. The larger signal at δ 4.68, a complex multiplet, appeared to be altered by irradiation at δ 2.22 and also at δ 2.06. Thus, the δ 4.68 signal is considered to arise from the remaining diastereotropic proton at e plus the methylene protons of some alkyl chains that are not branched at the β position (see degradation products below).

The small doublet at δ 1.04 was not collapsed by irradiation of any of the peaks downfield from the methylene envelope at δ 1.4, and hence it is presumably coupled to a proton in that envelope. The small difference in chemical shift between the δ 1.4 and 1.04 peaks precluded definitive verification of this point. By integration the small methyl doublet corresponds to slightly less than one-third the area of the larger doublet at δ 0.92.

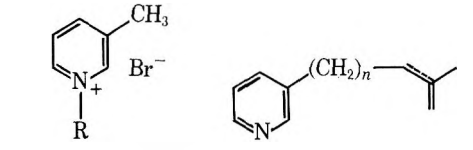
The multiplicity (triplet) of the two-proton, benzylic-type signal at δ 2.92 (coupled to δ 1.76) showed that the initial segment of the alkyl chain at C-3 of the pyridinium ring consists of two contiguous methylene groups. Combination of the foregoing data leads to the partial structure shown on Figure 1.

The absence of terminal methyl groups in halitoxin was indicated by the absence of the typical triplet in the region above 1.0 ppm in the 100 MHz spectrum, and this was confirmed by analysis at 360 MHz where the methyl doublet signals are well separated and no other absorptions are observed in this region. The ^1H NMR spectra also clearly show that there are no pyridine rings in which the nitrogen is not quaternized since even in the presence of base no peaks occur in the region where the aromatic protons of a free 3-alkylpyridine typically resonate. These facts suggest that the terminus of the alkyl chain at C-3 of one pyridinium ring is bonded to the nitrogen of another to give an oligomeric or polymeric structure as shown in formula 1.

The ^{13}C NMR data are in agreement with the proposed structure. Five low-field carbon resonances are observed (δ 149.5, 144.6, 144.0, 142.4, and 128.5), and these coincide with those of the model salts 2 and 3. The signal for the methylene carbon bonded to the quaternary nitrogen in halitoxin and 2 occurs at nearly the same position (δ 67.8 and 69.0), while the analogous carbon in 3 absorbs at slightly higher field (δ 6.19), as expected for a branched vs. straight chain structure.[10] The remainder of the ^{13}C NMR signals occurs at less than 36 ppm,

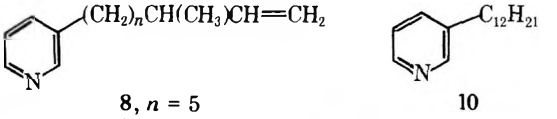


1 (n = 2, 3, 4, 5)



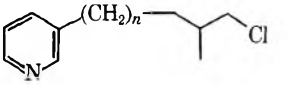
2, R = $CH_2CH(CH_3)_2$
3, R = $(CH_2)_{15}CH_3$

4, n = 4
5, n = 5
6, n = 6
7, n = 7



8, n = 5
9, n = 7

10



11, n = 5
12, n = 6

confirming that there are no carbons bearing hydroxyl groups in halitoxin.

Halitoxin was treated under a variety of conditions to probe for chemical functionality. Treatment with acetic anhydride in pyridine or triethylamine, with acetic anhydride/boron trifluoride etherate,[11] or with acetic–formic anhydride[12] did not cause any acetylation or formylation, and so provided chemical evidence for the lack of hydroxyl groups. Reaction with aqueous methanolic base (NaOH or K_2CO_3) produced intractable brownish gums, whereas the toxin was recovered unchanged after heating with aqueous methanolic hydrochloric acid. Halitoxin reacted with sodium borohydride or sodium dithionite, but gave unmanageable reduction products. Halitoxin readily formed precipitates with picric acid,

Table II. ^{1}H NMR Data for 3-Alkenylpyridines from Halitoxin from *H. rubens* Collected by GC

	GC fraction (Table III)								
	A	B	C	D	E	F	G	H	I
	Compound								
^{1}H NMR, δ	4/8	8	5	6	9	7	10/?	11	12
8.21, 7.36, 7.04 (pyr ring protons)	+	+	+	+	+	+	+	+	+
4.96 (t) (-CH_2CH=C(CH_3)$_2$)	+		+	+		+			
4.50 (-C(CH_3)=CH_2)									
4.86 (dd, J = 10, 1)	+	+			+		+		
4.89 (dd, J = 18, 1)									
5.6 (m) (-CH_nCH=CH_2)									
1.56 (-C(CH_3)=CH_2)	+		+	+		+			
1.46, 1.56 (-CH=C(CH_3)$_2$)									
0.96 (-CH(CH_3)-)	+	+			+			+	+
3.4 (dd, 6.1) (-CH(CH_3)CH_2Cl)								+	+

sodium tetraphenylborate,[13] or chloroplatinic acid. Of these salts, only the picrate was purified by redissolution, but that with considerable loss of material.

Dealkylation of halitoxin by heating with ethanolamine[14] was attempted but was unsuccessful under conditions which smoothly dealkylated a model compound, 3-carbamoyl-1-hexadecylpyridinium bromide. Attempts to break the quaternary ammonium structure via elimination were unsuccessful using alcoholic base, potassium *tert*-butoxide in dimethyl sulfoxide, diazabicyclooctane, and a conventional Hofmann elimination procedure.

Halitoxin was successfully degraded by pyrolysis. Heating at 140–160 °C decomposed the toxin and yielded a mixture of 3-alkenylpyridines and 3-(ω-chloroalkyl)pyridines, Tables I–III. The pyrolysis products were analyzed by combined gas chromatography–mass spectrometry (electron impact and chemical ionization) and also by ^{1}H NMR and MS analyses of fractions isolated by preparative gas chromatography. These results are summarized in Tables I and II.

The ^{1}H NMR spectrum of the residue from the pyrolysis is comparable to that of the toxin itself, except that the peaks are all very broad and the aromatic proton signals are shifted upfield slightly.

In the electron impact mass spectra, intense peaks were observed for all of the pyrolysis products at *m/e* 92, 93, and 106, indicative of a pyridine ring plus one and two methylene groups, respectively. One of these peaks was always the base peak. The electron impact spectra showed molecular ions for all of the components except those containing chlorine (peaks I and J). The chemical ionization spectra showed strong $(M + 1)^+$ and $(M + 29)^+$ peaks for all components including those containing chlorine.

The ^{1}H NMR spectra of fractions C, D, and F (Table II) clearly show that these samples are mixtures containing double-bond isomers, the difference occurring in the chain-terminating feature: isopropenyl vs. isopropylidene. Decoupling experiments on component C confirmed the olefinic methyl chemical shift assignments. This ^{1}H NMR data in conjunction with mass spectral analysis permits the assignment of the structures **5**, **6**, and **7** to these fractions.

Fraction A contains the signals for the isopropenyl/isopropylidene mixture, and in addition it contains signals appropriate for a terminal vinyl group (δ 4.86, 4.89, and 5.6). Since the mass spectrum shows a predominant molecular ion at 189 and a minor one at 203, this fraction is judged to contain predominantly alkenylpyridine **4** with a little of compound **8**.

Components B and E show ^{1}H NMR signals for a secondary methyl and a terminal vinyl group. The pattern for the nonterminal olefinic proton closely resembles that of 3-methyl-1-butene and indicates that the methyl group is on the allylic carbon. With molecular weights of 203 and 231, components B and E are assigned structures **8** and **9**, respectively. It was not possible to assign the position of the methyl group conclusively on the basis of the mass fragmentation pattern.

Fraction G has not been identified conclusively. It is an alkenylpyridine with two degrees of unsaturation in its side chain.

The chemical ionization mass spectra show that peaks H, I, and J, contain chlorine. The ^{1}H NMR spectra of peaks H and I lack olefinic proton absorption, but they do have signals for a secondary methyl group and a methylene group deshielded by chlorine. These data and the molecular weights established by mass spectrometry suggest structures **11** and **12** for the components H and I. Only mass spectral data is available for fraction J, and this indicates a molecular formula corresponding to the hydrochloride of either **7** or **9**.

Since there were no olefinic proton or vinyl methyl signals in the ^{1}H NMR spectrum of halitoxin, the unsaturation sites in the 3-alkenylpyridines clearly mark the sites of the nitrogen–alkyl links in the toxin. Since halitoxin also lacks quaternary methyl and isopropyl groups (^{1}H NMR), all of the alkyl chains must be joined through a terminal methylene group to the nitrogen. The isopropylidene groups in the pyrolysis products probably arise by acid-catalyzed isomerization of the initially formed isopropenyl group, the acid coming from the elimination. This supposition was corroborated when it was observed that the product from pyrolysis of halitoxin in the presence of powdered potassium carbonate contained signals only for an isopropenyl group.

The chemical and spectral data indicate an oligomeric or polymeric structure for halitoxin as shown in **1**. We propose that the toxin is a complex mixture containing molecules of different sizes, and with random variation in the length and structure of the alkyl chains linking the pyridinium rings.

We feel that at least for the 500–1000 molecular weight range materials the evidence indicates an overall macrocyclic structure containing 4–6 alkylpyridine units. This conclusion is based on the following arguments. First, there is no evidence for any nonquaternized pyridine rings in the ^{1}H NMR spec-

Table III. % Composition of Halitoxin Pyrolysis Products by GC Analysis

Halitoxin sample	Fractions, %										All others
	A	B	C	D	E	F	G	H	I	J	
H. rubens[a] (crude)	4 (15.8)[b]	6 (17.5)	26 (21)	18 (25.4)	9 (26.5)	7 (29.8)	~1 (38)	10 (40.5)	9 (47.5)	6 (55.5)	
H. rubens[a] (crude + K_2CO_3)	6	0.7	23	19	3	0.8	1	23	16	5	3
H. rubens[c] (500–1000)	0.7	1	15	13	3	1.6	2.6	27	14	10	13
H. rubens[c] (1000–25 000)	0.4	0.7	20	15	3	1	2.5	20	13	10	14
H. rubens[c] (>25 000)	0.4	1	18	15	3	2	2	22	16	10	11
H. erina[d]	10	10	33	24	1	1	1.3	5	14	3	

[a] A 6 ft × 1/8 in 10% FFAP on Chromosorb W, AW-DMCS, 60–80 mesh column; programmed at 170–230 °C (2 °C/min); initial flow rate, 20 mL/min. [b] Representative retention times in minutes. [c] A 6 ft × 1/8 in 3% OV-225 on Gas Chrom Q, 100–120 mesh, column; programmed at 100–240 °C (2 °C/min). [d] A 6 ft × 1/8 in 10% Carbowax 20M/2% KOH column; programmed at 150–230 °C (2 °C/min).

trum, even when it is measured in the presence of base. Secondly, there appear to be no alkyl chains terminating in methyl or isopropyl groups judging from a ^1H NMR spectrum (360 MHz) of the toxin itself and the structures of the pyrolysis products. In the absence of the saturated C terminal chains and nonquaternized pyridine rings, a macrocyclic structure is inferred. Phosphate or sulfate links between the pyridine nitrogen and the alkyl groups to form macrocyclic rings are possible, but we think that such structures are contraindicated by ^1H and ^{13}C NMR data on the 500–1000 molecular weight range fraction and by the low and variable sulfur and phosphorus contents observed.

As expected for an alkylpyridinium salt, halitoxin undergoes complete reduction upon hydrogenation with platinum catalyst; the NMR spectrum of the product is completely free of aromatic absorption. Field desorption mass spectral analysis of the reduction product from the 500–1000 molecular weight fraction showed a number of ions in the region *m/e* 811–963, consistent with a tetrameric structure, but it was not possible to see conclusively if there was a series of ions corresponding to higher oligomers.

In order to determine if halitoxin has the same composition in different species and in the different molecular weight range fractions, crude samples from *H. rubens* and *H. erina*, as well as the three different molecular weight range fractions from *H. rubens*, were pyrolyzed and the product compositions compared. One pyrolysis of crude halitoxin from *H. rubens* was carried out in the presence of powdered potassium carbonate to minimize any acid-catalyzed rearrangements. The composition of these pyrolysis products is summarized in Table III. The same major degradation products are observed in each case, but with some variation in the relative amounts of individual products. Minor variation in product composition was also noted on duplicate pyrolyses of a given fraction. The results indicate that halitoxins from the two species and all of the different molecular weight range fractions have essentially the same composition. The predominant monomer units in halitoxin are those corresponding to the alkenylpyridines **5** and **6**. These two products and their corresponding halides **11** and **12** account for nearly 50% or more of all the pyrolysis products in each case.

Table IV lists the different species of *Haliclona* that we have examined for halitoxin content and summarizes the toxicity and cytotoxicity data for the crude aqueous alcohol extracts of these sponges. The presence of halitoxin was ascertained by ^1H NMR analysis of the 1-butanol-soluble fraction from workup of the sponge extracts. In addition to cytotoxicity and toxicity to mice, halitoxin caused haemolysis

Table IV. Occurrence of Halitoxin in *Haliclona* Species and Bioactivity of Crude Aqueous Alcoholic Extracts

Species	Halitoxin	KB	LD_{50}, mg/kg
H. rubens	+	7.0	5
H. viridis	+	2.8	2–3
H. erina	+	2.8	3
Haliclona sp.	+	26	~3
H. permallis (?)	−	100	Not toxic

at a threshold concentration of 1 μg/mL. Water containing 100 μg/mL of crude halitoxin (1-butanol soluble) or halitoxin purified by cation exchange chromatography was toxic to goldfish (survival times, 40 and 25 min, respectively). Out of 15 microorganisms tested, halitoxin showed significant antibiotic activity against only two, *Bacillus subtillus* and *Streptococcus pyogenes*, both gram-positive organisms.

We have thus far been unable to detect in the sponge extracts any simple alkylpyridine derivatives that might be likely precursors of halitoxin.

Two N-methylated pyridine salts, homarine[15] and trigonelline,[15,16] have been isolated from sponges, but halitoxin appears to be the first marine pyridinium salt in which a long chain alkyl group alkylates the nitrogen. Other pyridine alkaloids of marine origin with 3-alkenyl substituents include anabasine[17] from a nemertine worm and navenone-A,[18] one component of a trail-breaking alarm pheromone from an ophistobranch mollusc. The side chain length in navenone-A resembles those found in halitoxin. The predominant methyl-branched 3-alkyl substituents linking the pyridinium rings in halitoxin are identical in structure with the alkyl portion of muscopyridine.[19]

Experimental Section[20]

Isolation of Halitoxin from Freeze-Dried Sponge. *Haliclona rubens* from near Isla Maguayez, P.R., Dec 1974, was freeze-dried shortly after collection to give 83.5 g of dry sponge. This was extracted continuously with methanol for 14 h. Evaporation of the methanol yielded 29.3 of residue, which was suspended in water and extracted with three 200-mL portions of dichloromethane. The aqueous solution then was extracted with three portions of 1-butanol (400 mL and 2 × 200 mL). Evaporation of the combined 1-butanol solution gave crude halitoxin (3.09 g).

Isolation of Halitoxin from Air-Dried Sponge. *H. rubens* collected at Isla Maguayez, P.R., May 1972, was air-dired. A 1.03-kg batch was powdered in a blender and defatted by continuous extraction with chloroform for 2 days in a Ciereszko[21] apparatus to yield 45.6 g of chloroform extract. The marc was dried in a current of air and then extracted continuously with methanol for 3 days. The methanol extract was concentrated at reduced pressure, water was

added to give 1400 mL, and the aqueous solution was extracted with three portions (500 mL and 2 × 300 mL) of 1-butanol. Evaporation of the combined 1-butanol solution afforded crude halitoxin (51.1 g).

Ultrafiltration. A 3.18-g sample of crude halitoxin from *H. rubens* was dissolved in water and filtered under nitrogen pressure through a 500 nominal molecular weight limit membrane (Diaflo UM05, Amicon Corp., Lexington, Mass.). Lyophilization of the filtrate gave 0.472 g of residue (<500 molecular weight material). The retentate was diluted with water and similarly filtered through a 1000 molecular weight limit membrane (Pellicon PSAC, Millipore Corp., Bedford, Mass.). The filtrate was lyophilized to yield 0.762 g of residue which constitutes the 500–1000 molecular weight range fraction. The retentate was lyophilized, and a 0.700-g portion of it was redissolved in water and filtered through a 25 000 molecular weight limit membrane (Pellicon PSED). Lyophilization of both filtrate and retentate afforded residues weighing, respectively, 0.100 (1000–25 000 molecular weight range fraction) and 0.600 g (>25 000 molecular weight range fraction). At each stage of the ultrafiltration, the retentate was diluted and the ultrafiltration was repeated two times using the same membrane to insure that all materials of molecular weight less than the membrane's nominal molecular weight cutoff range had passed into the filtrate.

Purification of Halitoxin via Picrate Formation. An aqueous solution of the toxin (500–1000 molecular weight range, 14.6 g) was passed through a column (3.8 × 40 cm) of anion exchange resin (Bio-Rad AG-21K) which had been prewashed with a picric acid solution.[22] The cloudy eluate was lyophilized to give 16.5 g of picrate. The picrate could not be recrystallized, but it was purified somewhat by repeated trituration (total volume 800 mL) with hot acetone. The acetone solubles were treated with charcoal and the solvent evaporated to give 5.81 g of picrate. Picrate complex was also formed by addition of halitoxin to a saturated solution of picric acid in ethanol.

Acetone and then 1 M hydrochloric acid were added to 5.8 g of picrate, and the mixture was stirred while being heated on a steam bath. The solution was decanted from the insoluble picrate, which was washed twice more in like manner. The combined washings were extracted three times with ether, and the aqueous solution was lyophilized to give 3.21 g of halitoxin (chloride form).

Halitoxin Chloride via Anion Exchange. A 1.00-g sample of halitoxin, 500–1000 molecular weight, was dissolved in water (20 mL), and the solution was divided into two equal volumes. One of these was passed through a column of 13.5 g of AG-21K chloride form resin (Bio-Rad Laboratories, Richmond, Calif.). The column was washed with water, and the combined aqueous solution was lyophilized to yield a light brown powder.

Anal. Calcd for $C_{15}H_{24}NCl{\cdot}2H_2O$ (av): C, 62.3; H, 9.6; N, 4.8; Cl, 12.1. Found: C, 61.90; H, 8.12; N, 6.45; Cl, 11.14.

The remaining half of the original solution was lyophilized to yield a similar substance.

Anal. Calcd: see above. Found: C, 61.94; H, 8.16; N, 6.39; Cl, 9.24.

Halitoxin (brown powder): IR (thin film) 3495 (H_2O), 3040, 1630 (pyridinium) cm^{-1}; UV λ_{max} (95% ethanol) 267, inflection at 273 nm; ^1H NMR (CD_3OD) δ 0.92 (3 H, d, J = 7 Hz), 1.04 (ca. one-third the area of δ 0.92 peak, d, J = 7 Hz), 1.4 (~10 H, brd s), 1.76 (brd m), 2.22 (brd m, coupled to δ 0.92 and ~4.5), 2.93 (2 H, t, J = 7 Hz), 4.3–4.8 (m, partially obscured by HOD peak), 8.11 (1 H, t, J = 7 Hz, pyr C-5), 8.56 (1 H, d, J = 7 Hz, pyr C-4), 8.93 (1 H, d, $J \cong 6$ Hz, pyr C-6), 9.05 (1 H, brd s, pyr C-2); ^1H NMR (CD_3OD/C_5D_5N) δ 4.4–5.0, HOD peak at δ 5.1); ^1H NMR ($CD_3OD/C_5D_5N/D_2O/Na_2CO_3$) aromatic region at δ 8.12 (t), 8.56 (d), 8.92 (brd s overlapping d); ^1H NMR (360 MHz, CD_3OD) δ 0.92 (3 H, d, J = 7 Hz), 1.04 (d, J = 7 Hz, one-third the area of δ 0.92 peak), 1.4 (~15 H, brd s, $-CH_2-$), 1.76 (~3 H, brd s coupled to δ 2.92), 2.06 (1 H, brd s coupled to δ 4.68), 2.22 (1 H, brd s coupled to δ 0.92, 4.42 and 4.68), 2.92 (2 H, t, $J \cong 7$ Hz), 4.42 (1 H, dd, $J \cong 8$ and 12 Hz), 4.68 (~2 H, m), 8.08 (1 H, pyr C-5), 8.52 (1 H, pyr C-4), 8.9 (1 H, pyr C-6), 9.0 (1 H, brd s, pyr C-2); ^{13}C NMR (Me_2SO-d_6/D_2O) δ 145.9, 144.6, 144.0, 142.4, 128.5, 67.8, 35.8, 33.6, 32.9, 30.5, 29.3, 28.9, 26.5, 17.0.

Anal. Calcd: see above. Found: (*sample purified by cation exchange*) C, 64.80; H, 8.70; N, 5.12; Cl, 11.08; others (S, 1.33, 0.9; P, 0.3, 1.23).

Pyrolysis of Halitoxin. (a) From *H. rubens*. A 2.16-g sample of halitoxin was placed in a 25 mL round-bottom flask fitted with a Kugelrohr receiver. The apparatus was evacuated to 0.005 mmHg, and the flask was heated at 160–170 °C for 4 h. A yellow oily pyrolysate (1.33 g, 62%) was obtained. For ^1H NMR, MS, and GC analyses, see Tables I–III. ^1H NMR analysis of the pyrolysis residue: (CD_3OD) δ 8.40, 7.66, 7.36, 4.88, 2.64, 1.34–3.1 (several humps), 1.34 (large brd s), 0.96.

(b) From *H. erina*. A 530-mg sample of the 500–1000 nominal molecular weight range fraction of halitoxin from *H. erina* was heated in a Kugelrohr apparatus at 150–165 °C and 0.02 mmHg for 90 min. A yellow oily distillate (325 mg, 61%) was obtained, leaving a black pot residue (135 mg, 25%). Loss of water probably accounts for the 14% lost. For MS and GC analyses, see Tables I and III.

Pyrolysis in the Presence of Base. A mixture of halitoxin (500 mg) from *H. rubens* and potassium carbonate (5.0 g) was ground to a fine powder and then heated at 168 °C and 0.01 mmHg for 4 h. A brown distillate (157 mg, 31%) was obtained. For GC analysis, see Table III.

Hydrogenation of Halitoxin. A suspension of 150 mg of platinum oxide in 2 mL of methanol was stirred under hydrogen for 15 min, and then a solution of 99 mg of halitoxin (purified via picrate formation, 500–1000 molecular weight, from *H. rubens*) in 3 mL of methanol was added. After being stirred at room temperature and atmospheric pressure for 18 h, the suspension was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane/diethylamine (9:1) and passed through a short column of Silicar CC-7 (fine mesh). The column was washed with the same solvent, and the combined eluate was evaporated to give a colorless viscous residue (28.5 mg): ^1H NMR (100 MHz, $CDCl_3/CD_3OD$) (integral based on assumption of 6 H at δ 3.02) δ 1.00 (~2 H, d), 1.28 (brd s), 1.38 (brd s) (total area δ 1.20–1.60, ~16 H), 1.80 (brd s, ~4 H), 3.02 (brd d, 6 H), 4.58 (s, HOD); field desorption mass spectrum (prominent ions) m/e 364, 484, 575, 595, 629, 643, 811, 825, 839, 853, 864, 867, 880, 881, 963.

1-Isobutyl-3-methylpyridinium Bromide (2). The salt **2** was prepared by the reaction of isobutyl bromide with β-picoline in methanol. The crude product was dissolved in water and washed with benzene to remove unreacted material. Lyophilization of the aqueous solution gave 1-isobutyl-3-methylpyridinium bromide as a hygroscopic crystalline mass: IR (KBr) 3010, 2940, 1640, 1510, 1475 cm^{-1}; ^1H NMR [$CDCl_3/CD_3OH$ (1:1)] δ 9.08–8.76 (2 H, m), 8.46 (1 H, d, J = 8 Hz), 8.10 (1 H, m), 4.59 (d, J = 7 Hz; also HOD), 2.68 (3 H, s), 2.41 (1 H, heptet, J = 7 Hz), 1.05 (6 H, d, J = 7 Hz); ^{13}C NMR (Me_2SO/D_2O) δ 146.3 (d), 144.0 (d), 141.6 (d), 140.0 (s), 127.7 (d), 69.0 (t), 31.3 (d), 19.6 (q, $2CH_3$), 19.0 (q).

A picrate prepared in the usual manner and recrystallized from aqueous methanol melted at 118–120 °C.

Anal. Calcd for $C_{16}H_{18}O_7N_4$: C, 50.79; H, 4.80; N, 14.81. Found: C, 50.61; H, 4.80; N, 14.73.

1-Hexadecyl-3-methylpyridinium Bromide (3). Reaction of cetyl bromide with β-picoline followed by purification as described for **2** gave **3** as a white powder, mp 44–48 °C, after one recrystallization from benzene/hexane: IR (KBr) 2920, 2840, 1640, 1505, 1475, cm^{-1}; ^1H NMR [$CDCl_3/CD_3OD$ (1:1)] δ 9.02–8.72 (2 H, m), 8.43 (1 H, d, J = 8 Hz), 8.05 (1 H, m), 4.70 (m; also HOD), 2.65 (3 H, s), 2.08 (2 H, brd m), 1.28 (26 H, brd), 0.90 (3 H, t, J = 3 Hz); ^{13}C NMR (Me_2SO/D_2O) δ 146.3 (d), 144.0 (d), 142.0 (d), 139.8 (s), 128.1 (d), 61.9 (t), 32.9, 32.3, 30.9 (several CH_2), 26.9 (t), 23.3 (t), 19.0 (q), 14.6 (q).

Picrate mp 68–69 °C, after one recrystallization from methanol.

Anal. Calcd for $C_{28}H_{42}O_7N_4$: C, 61.52; H, 7.56; N, 10.25. Found: C, 61.53; H, 7.56; N, 10.20.

Acknowledgment. We are grateful for the use of the University of Puerto Rico Marine Laboratory, Isla Maguayez. We thank Drs. L. S. Ciereszko and R. E. Schroeder for collection of some samples, Dr. C. Shew, R. S. Kerr Environmental Research Laboratories, Ada, Okla. for performing GC/MS analyses, and Dr. K. L. Rinehart, University of Illinois, for providing a field desorption mass spectrum. The 360 MHz NMR spectra were obtained from the Stanford Magnetic Resonance Laboratory supported by a grant from the Biotechnology Resources Branch of the National Institutes of Health. We gratefully acknowledge grants from the Phillips Petroleum Co., Bartlesville, Okla., and the National Science Foundation (GP 38410), which aided in the purchase of spectrometers. Antibiotic testing was kindly provided by the Upjohn Co., Kalamazoo, Mich.

Registry No.—**2**, 66902-16-7; **2** picrate, 66902-18-9; **3**, 2315-39-1; **3** picrate, 66902-19-0; **4**, 66902-08-7; **5**, 66902-10-1; **6**, 66902-11-2; **7**, 66902-13-4; **8**, 66902-09-8; **9**, 66902-12-3; **11**, 66902-14-5; **12**, 66902-15-6; halitoxin-R, 54990-72-6; isobutyl bromide, 78-77-3; β-picoline, 108-99-6; cetyl bromide, 112-82-3.

References and Notes

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Biosynthetic Studies of Secondary Plant Metabolites with $^{13}CO_2$. *Nicotiana* Alkaloids. 2.[1] New Synthesis of Nornicotine and Nicotine. Quantitative Carbon-13 NMR Spectroscopic Analysis of [2′,3′,*N*-CH_3-$^{13}C_3$]Nicotine[2]

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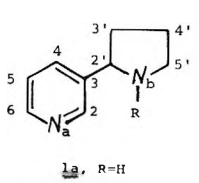
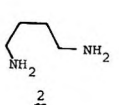
An efficient synthesis of the tobacco alkaloids, nornicotine (**1a**) and nicotine (**1b**), is achieved by Michael condensation of the α-lithiomethoxime of 3-acetylpyridine (**11**) with a ketene thioacetal monoxide (**4**) to give **12a**, thus providing all the pyrrolidine ring atoms of **1a** in masked form. Subsequent reduction with diborane and reductive cyclization in refluxing 97% formic acid are used to produce *N*-formyl-**1a** in high yield. The latter is converted to **1a** or **1b** by literature procedures in 60% overall yield from 3-acetylpyridine. The chemistry of several alternative, but inefficient, synthetic approaches to **1a** also is discussed, in particular a route from 3-acetylpyridine and mesylaziridine (**16**). The synthesis of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** is achieved by this route from [1,2-$^{13}C_2$]acetic acid and [^{13}C]formaldehyde via [1′,2′-$^{13}C_2$]-3-acetylpyridine. Analysis of the proton-decoupled ^{13}C NMR spectrum of the triply ^{13}C-labeled **1b** is done to certify the accuracy of the quantitative determination of the relative ^{13}C enrichment in **1b** biosynthetically labeled by $^{13}CO_2$. Thereby an earlier conclusion about the symmetry of ^{13}C labeling of carbons 2′ and 5′ of **1b** is circumstantially validated, i.e., that these four carbons are unequally ^{13}C labeled by $^{13}CO_2$ within experimental error.

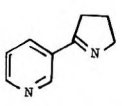
We are studying the applicability of highly enriched $^{13}CO_2$ as a biosynthetic probe of secondary plant metabolites, particularly alkaloids. In our first paper concerning the tobacco alkaloids[1] the results of some initial feeding experiments using 97 atom % $^{13}CO_2$, in which we studied the biosynthesis of nicotine (**1b**), the major alkaloid of *N. tabacum* and *N. glutinosa*, were described and *tentatively* interpreted as corroborating some of Rapoport's earlier observations obtained with $^{14}CO_2$:[4] that the *N*-methylpyrrolidine ring of **1b** could become unsymmetrically labeled by incorporation of isotopically labeled CO_2. Since such conclusions are in variance with all of the other data concerning nicotine's biosynthesis,[1,5] i.e., that the *N*-methylpyrrolidine ring of **1b** is formed in vivo via putrescine (**2**) and thereby should be symmetrically labeled by isotopic carbon labeled precursors, it is very important to certify the experimental error of our technique of ^{13}C label distribution analysis (^{13}C NMR spectroscopy). This is especially important since the intramolecular ^{13}C labeling inequality of **1b** that we reported was C(2′) (62%), C(3′) (65%), C(4′) (58%), and C(5′) (49%),[1] such values perhaps being equivalent within experimental error, although Matwiyoff and Burnham had certified that the technique we used was accurate to within ±1.4% for uniformly and nonuniformly ^{13}C-labeled acetate.[6] For this reason we developed a new synthesis of nornicotine (**1a**) and **1b** designed to meet our special needs for the synthesis of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b**. The chemistry that was encountered during the development of our most efficient synthetic route to **1a** and **1b** is reported here as well as the synthesis and quantitative ^{13}C NMR spectroscopic analysis of the triply ^{13}C-labeled **1b**. From our new results the earlier



1a, R=H
b, R=CH_3



2



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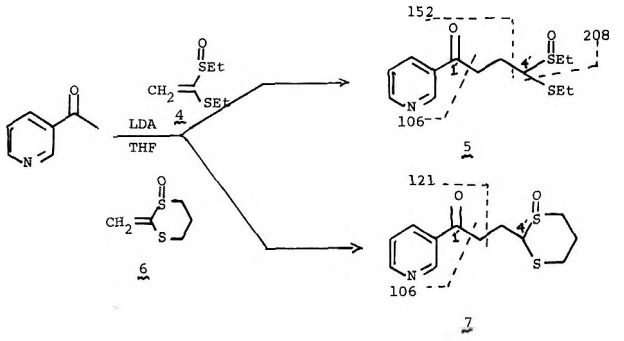
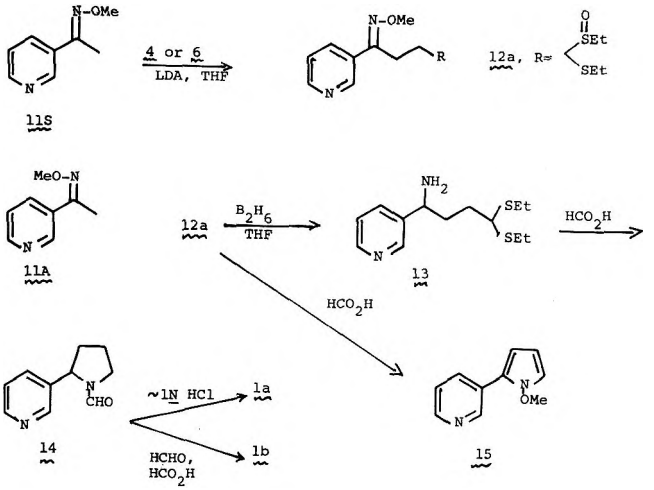
Scheme I



Scheme II

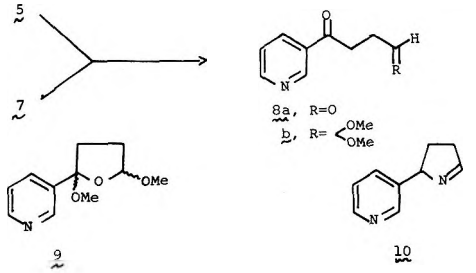


conclusion about the labeling of **1b** by $^{13}CO_2$[1] is partly validated.

Results and Discussion

I. The Synthesis of Nornicotine (1a) and Nicotine (1b). The several syntheses of **1b** reported to date[7] have two general strategies. The most frequently used synthetic route has been the one in which pyridine with a one-carbon C(3) substituent at various oxidation levels is condensed with a three-carbon equivalent. The *N*-CH_3 group is either contained in the three-carbon unit or introduced by reductive amination of a 1,4-dicarbonyl intermediate. The most novel syntheses of **1b** are Leete's biogenetically modeled route,[7h] and Steven's cyclopropylimine rearrangement route,[8a] which gives myosmine (**3**), a minor tobacco alkaloid easily converted into **1b** by reduction and reductive *N*-methylation.[7i,9] None of these strategies was felt to be applicable to our special needs for the synthesis of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** either due to their low overall yields or to the limited commercial availability of a suitably ^{13}C-labeled starting material. Hence we chose to develop an alternative strategy wherein the *N*-methylpyrrolidine ring of **1b** is constructed from 3-acetylpyridine methoxime (**11**), Schlessinger's[10] ketene thioacetal monoxide (**4**), and formaldehyde by Eschweiler–Clarke reductive methylation. The same strategy is employed in a different tactical development in which 3-acetylpyridine and mesylaziridine (**16**) are used to synthesize **3**. In either case our initial assumption was that the desired ^{13}C labeling of **1b** could be achieved straightforwardly by synthesis of doubly ^{13}C-labeled 3-acetylpyridine from [1,2-^{13}C]acetic acid and reductive methylation using [^{13}C]formaldehyde.

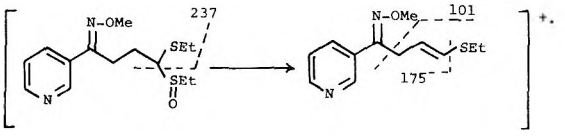
Ketene thioacetal monoxides **4** and **6** (Scheme I) were prepared by a convenient modification of Schlessinger's procedure[10a] in 69 and 57% overall yield, respectively (Experimental Section). Condensation of **4** with the lithium enolate (from lithium diisopropylamide) of 3-acetylpyridine occurred at −10 °C in THF overnight, giving **5** in 38% yield; similiarly **7** was obtained in 46% yield using **6**. The structures of **5** and **7** were consistent with the principal spectral data: characteristic ^1H NMR signals for the pyridyl and C(4′) thioacetal protons and electron impact mass spectral fragments as indicated in Scheme I. Sodium hydride also could be used as the base in THF/HMPA solvent mixtures at −78 °C, but the yield of **5** was much lower than with LDA and dialkylation of 3-acetylpyridine appeared to be a serious problem. It also was noticed that in the formation of **5** prolonged reaction times resulted in the reappearance of starting materials (TLC), indicating that the reaction was partially reversible under the conditions we used.



Hydrolysis of **5** or **7** to the 1,4-dicarbonyl compound (**8a**), followed by reductive amination, was anticipated to lead to **1a** or **1b**. Both **5** and **7** were resistant to hydrolysis with aqueous acid/CH_3CN,[10] aqueous acid/$HgCl_2$, boron trifluoride etherate/HgO,[11] or boron trifluoride etherate/$Hg(OAc)_2$ in acetic acid.[11] By treatment of **5** with $HgCl_2$ and *p*-toluenesulfonic acid in methanol at room temperature for 24 h the desired hydrolysis could be achieved but in very low yield: **8a** (11%) and **8b** (15%).[12] Since the major byproduct under these conditions was the tetrahydrofuran (**9**),[12] attempts were made to reductively aminate the carbonyl of **5**. We assumed that during the subsequent hydrolysis the primary amine would more effectively trap the incipient C(4′) carbonium ion than the solvent molecules to give isomyosmine (**10**), which would be reducible to **1a** by precedent.[7i,9] However, treatment of the hydrochloride salt of **5** with $NH_4Br/NaCNBH_3$[13] or its oxime with $NaCNBH_3$ at pH 3[13] did not give any of the desired products; overreduction of the pyridine ring and poor material balance in the reaction resulted instead.

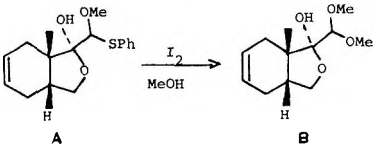
In view of these disappointing results a different approach to **1a** and **1b** was investigated. Since the low yields in the formation of **5** were felt to be due in part to the condensation's reversibility, we considered the use of α-lithio-3-acetylpyridine methoxime (**11**) as the nucleophilic partner. Spenser and Leong[14] had reported that the methoxime of dibenzyl ketone was deprotonated and regiospecifically deuterated on the syn α carbon. Similar observations have been described about ketoxime dianions,[15,16] which are stabler than methoxime monoanions,[15] although Kofron and Yeh reported that dilithioacetone oxime did not give 1,4 adducts with acrolein, only aldol condensation products in low yield.[16] We reasoned that the α-monoanion of **11** would be a more reactive nucleophile than α-lithio-3-acetylpyridine and, because of the lower acidity of **11** than 3-acetylpyridine, would disfavor the reversibility of the 1,4 addition to **4**. Methoxime **11** was shown to be composed of two geometrical isomers in a ratio of 83:17 by the relative integrals of the *O*-CH_3 and pyridyl ring protons. Since the methyl carbon syn to the hydroxyl of 2-butanone ketoxime resonates at ~6–6.8 ppm higher field than the anti methyl carbon,[17] and since in geraniol the (*Z*)-4-CH_3 resonates at δ_C 16.0 relative to the (*E*)-4-CH_3 (δ_C 23.5) in nerol,[18] the more abundant compound in the **11** mixture must be the syn isomer (**11S**), δ_C 11.9, and the less abundant the anti isomer (**11A**), δ_C 20.8 (Scheme II). Michael addition of α-lithio-**11** to **4** proceeded readily in THF at −78 °C giving **12a**

(86–95%). Compound **12a** was only the C(1′) *E* isomer based on the chemical shift of its *O*-CH_3 protons at δ 3.99, since the methoxime prepared from **5** was a 74:26 mixture of the syn (δ_H 4.00) and anti (δ_H 3.85) isomers.[19] It had a mass spectral fragmentation pattern similar to **5.**



In accord with the known reduction of methoximes to primary amines[20] and sulfoxides to thioethers[21] using diborane, **12a** gave the amino thioacetal (**13**) in quantitative yield[22] by reduction with excess diborane in THF at 25–65 °C. When this reduction was carried out at 25 °C, **13** (40%) plus a second substance (21%) were obtained, the latter proving to be the *O*-methylhydroxylamine derivative of **13** based on its proton resonances at δ 3.40 (OCH_3), 3.76 (H-1′), and 3.98 (H-4′).

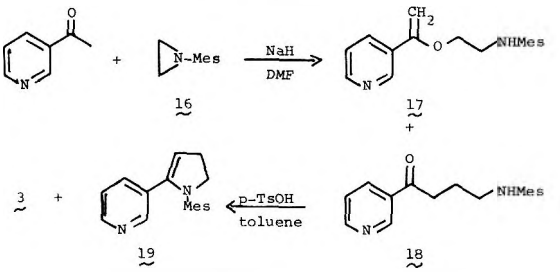
As with **5** the hydrolysis of **13** to a 4-amino aldehyde (or **10**) proved to be troublesome. Not surprisingly treatment of **13** in CH_3CN/H_2O with $HgCl_2$ resulted in the immediate precipitation of a mercuric complex, which did not give any of the desired products after 13 h at room temperature, nor after reduction of the crude reaction mixture with $NaBH_4$. The use of $CdCO_3$[23] or $CuO/CuCl_2$[24] gave only unreacted **13.** Hydrolysis through alkylation[25] or oxidation at sulfur[26] was not attempted because of the presence of primary amine and pyridine functionality and the sensitivity of the expected products to oxidation. Since Trost and Miller reported that the transacetalization A to B proceeded smoothly using I_2 in



refluxing methanol,[27] it was anticipated that **13** could be converted to **10** under similar conditions. Indeed, treatment of **13** with 2 equiv of I_2 in CH_3CN/H_2O at 25 °C for 1 h followed by appropriate workup gave **10** in 41–56% yield plus $(EtS)_2$, although **10** seemed to be quite sensitive to oxidation conditions since excess I_2 or silver oxide caused the formation of polar byproducts and markedly lowered the yield of **10.** The structure of **10** was fully consistent with its principal spectral characteristics: δ_H at 7.24 (q, H-5′) and 5.12 (t, H-2′); molecular ion at *m/e* 146. Reduction of **10** using $NaBH_4$ gave **1a** (66%), which also was obtained directly from **13** without isolation of **10** in 26% yield. The best overall yields of **1a** from **13** (30–40%) were obtained by using AcOH as the reaction solvent, in which evidence was obtained (^1H NMR) for the formation of an intermediate 4-amino diacetoxyacetal, although this substance was too unstable to isolate and characterize fully.

At this stage the capriciousness of the latter hydrolysis technique resulted in the loss of ~40% of our precious ^{13}C-labeled **13** (vide infra), causing us to consider yet another method for conversion of **13** to **1a**, which turned out to work very well. We reasoned that if formic acid was acidic enough to cause a small amount of **10** to form from hydrolysis and intramolecular cyclization of **13,** its well known propensity for imine reduction [28] would drive the reaction in the desired direction. Thus it was gratifying to observe the formation of **14** in 75% overall yield from **12a** when crude **13** was refluxed for 3 h in 97% formic acid.[29] *N*-Formyl-**1a** (**14**) had a doubled formyl proton resonance at δ 8.37 (0.4 H) and 8.10 (0.6 H) indicative of restricted rotation about its amide bond and an expected rapid loss of HCO from the molecular ion in its mass spectrum, giving a fragment ion at *m/e* 147. When **12a** was refluxed 1 h in 97% formic acid, the *N*-methoxypyrrole (**15**)

Scheme III



was formed in 54% yield[12] along with several other more polar compounds. Apparently, the resistance of the methoxime to reduction by HCO_2H in this case directs the reaction's course toward aromatized products, rather than toward *N*-OMe-**3** or -**1a.** Conversion of **14** to **1a** by refluxing in 3 N HCl[28] or to **1b** by Eschweiler–Clark reductive methylation[7i,28] was achieved in 91–93% yield. Furthermore, **1b** could be obtained in 66% overall yield from **12a** without isolation of any intermediates. The resulting overall yield of nicotine or nornicotine was 60% from 3-acetylpyridine, one of the best yielding syntheses of these alkaloids reported to date.[30]

During the initial stages of our work a synthesis of **1a** alternative to that shown in Scheme II was investigated briefly (Scheme III). Although the yield of **3** was too low to warrant further development, the observations are worth mentioning.

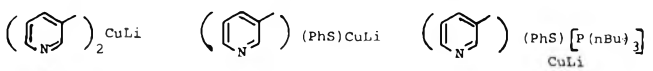
Alkylation of the sodium enolate of 3-acetylpyridine with mesylaziridine (**16**)[31] in DMF at 0 °C gave O-alkylated (**17**) and C-alkylated (**18**) products in a 1:1 ratio in only moderate yield (38%). The use of lithium (LDA in THF) or potassium (KO-*t*-Bu in *t*-BuOH) enolates was less successful than the former and did not markedly change the O to C alkylation ratio. One can conjecture that the presence of O-alkylation here in contrast to its lack using **4** or **6** as the electrophile can be rationalized according to the hard–soft acid–base principles.[32] Since **4** is predicted to be a softer electrophile than **16,** attack by the softer carbanion center of 3-acetylpyridine's enolate would be favored over attack by the harder oxyanion center, whereas with **16,** O-alkylation predominates. Solvent polarity differences also are an important factor here. When **18** was treated subsequently with 1 equiv of *p*-toluenesulfonic acid in refluxing toluene for 3 h with azeotropic water removal, two major products were formed: a mesylate, **19,** the expected product, in 26% yield, which was characterized by its ^1H NMR resonances at δ 2.81 (mesylate) and 5.73 (H-3′) and rapid loss of methanesulfinic acid upon mass spectral fragmentation; and myosmine (**3**) in 15% yield, identified spectrally and by reduction with $NaBH_4$ to **1a** in 66% yield. The appearance of **3** in this reaction was rather surprising, since mesylates usually are rather resistant to acid-catalyzed hydrolysis.

II. The Synthesis of [2′,3′,*N*-CH_3-$^{13}C_3$]Nicotine. A synthesis of [1′2′-$^{13}C_2$]-3-acetylpyridine was required for the synthesis of [2′,3′-$^{13}C_2$]nornicotine. The normal method used to synthesize 3-acetylpyridine, Claisen condensation of ethyl nicotinate and ethyl acetate followed by acid-catalyzed ester hydrolysis and decarboxylation,[33] was felt to be inexpedient and expensive since the ethyl acetate is used in large excess. One attempt was made to react 1 equiv of dilithioacetate with methyl nicotinate (THF at −78 to −30 °C), but the initial results were not encouraging so this route was abandoned. Consequently, we investigated the use of several of the literature methods for ketone synthesis,[34] which were based on the reaction of 3-lithiopyridine with a two-carbon electrophile. Such condensations had to be carried out at <−30 °C due to the instability of 3-lithiopyridine at higher temperatures.[35] However, when acetronitrile or lithium acetate were reacted with 3-lithiopyridine the heterogenous reactions did not proceed until −30 to −10 °C and in both cases the yields of

3-acetylpyridine were low (1–27%) and very poorly reproducible. The use of the more reactive acetylimidazole,[36] dimethylacetamide, or 2-pyridyl thioacetate[37] as electrophile in THF at ~ −50 °C was also unsuccessful, although a small amount of 3-acetylpyridine was formed with the first two reactants. We attribute these failures to the high basicity and low nucleophilicity of 3-lithiopyridine, which favored deprotonation of the electrophile rather than its nucleophilic arylation.

The ketone synthesis of Mukaiyama et al.,[37] in which Grignard reagents are acylated by 2-pyridyl thioacetate, was attempted using the Grignard reagent prpeared from a threefold excess of highly reactive magnesium[38] and 3-bromopyridine at 25 °C. No reaction occurred at 0–25 °C, which may have been due to the excess magnesium needed to prepare the Grignard reagent in good yield.

The use of the mixed cuprate(I) reagents, **20–22,** reported to yield ketones in good yield by reaction with acid chlorides,[39] initially appeared to be encouraging, since 3-benzoylpyridine was prepared from **22** (only; none of this ketone was formed



20 **21** **22**

using **20** or **21**) and benzoyl chloride in 67% yield.[12] However, the same reaction carried out with acetyl chloride failed to yield any 3-acetylpyridine, nor was any of this ketone obtained using **20** or **21.** Since lithium diorganocuprates are not as basic as organolithiums,[39b] the lack of 3-acetylpyridine formation probably is not due to deprotonation of acetyl chloride, but may be due to the difference in reduction potential of radical anion intermediates, *if* these reactions proceed by a two-stage mechanism as proposed by House for conjugate additions of lithium organocuprates.[39b,41]

Since all our attempted ketone syntheses via acetic acid derivatives had been fruitless, we next considered the synthesis of 3-ethylpyridine (**23**), since we had discovered that this could be oxidized to 3-acetylpyridine in 70–83% yield in buffered $KMnO_4$. We attempted to reproduce the synthesis of Giam[41] in which the dihydropyridine reagent prepared from $LiAlH_4$ in excess pyridine was reported to be alkylatable at C(3) by ethyl iodide in 89% yield (gas chromatographic analysis). In our hands this method worked with benzyl chloride as reported, giving 3-benzylpyridine in 24% isolated yield calculated from benzyl chloride, but 3-ethylpyridine was obtained in only 17% yield (GLC) despite several variations in experimental conditions, the major product being quaternized pyridine.[12] At this point we recalled that during the preparation of 3-lithiopyridine from *n*-butyllithium and 3-bromopyridine at −78 °C, a small amount of 3-*n*-butylpyridine usually was formed from alkylation of the *n*-butyl bromide produced in the initial transmetalation. Accordingly, we found that **23** was produced in 77% yield by reaction of ethyl iodide with 3-lithiopyridine at −95 °C. After we completed this work a paper by Parham and Piccirilli appeared in which was described the alkylation of 2- and 3-bromopyridine with *n*-butyl bromide under conditions identical with ours.[42]

Thus, the synthesis of [2′,3′,*N*-CH_3-$^{13}C_3$]nicotine was completed in good overall yield using the chemistry described above as shown in Scheme IV.

III. Quantitative ^{13}C NMR Spectroscopic Analysis of [2′,3′-*N*-CH_3-$^{13}C_3$]Nicotine. The procedures described in our earlier paper[1] were used to prepare samples of the N_b-monoethanesulfonate of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** for ^{13}C NMR analysis. It was found that care had to be taken to prepare such samples immediately after elution from the chromatographic adsorbent to avoid line-broadening effects in the carbon spectra. Since all paramagnetic ions extractable with dithiazone in CCl_4 were customarily removed, this line-broadening problem may have been due to oxidation of **1b** in which unpaired electron-containing species were generated in situ; however, as sample degassing by argon did not always alleviate this problem, our hypothesis is conjectural.

Table I. Relative Percentage ^{13}C Enrichment of [2′,3′,*N*-CH_3-$^{13}C_3$]Nicotine

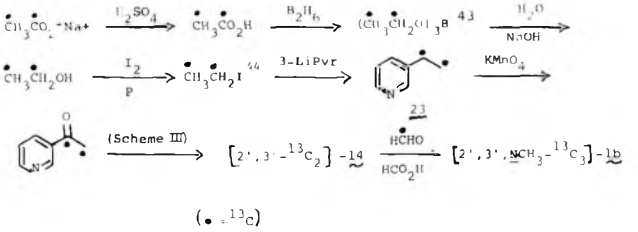
method	intramolecular[a] C(2′)	intramolecular[a] C(3′)	intermolecular[a] C(2′)	intermolecular[a] C(3′)	intermolecular[a] *N*-CH_3
mass spectral[b]	85.6 (89.6)	93.0 (90.8)	5.8	6.2	4.5
^1H NMR	86.1	93.0			
^{13}C NMR					
A[c]	90.9	92.8	6.6	7.5	5.7
B[d]	89.6	92.2	7.0	7.2	*e*
C[f,h]	91.8	94.0	*e*	*e*	*e*
D[g,h]	91.5	93.8	*e*	*e*	*e*

[a] The precision of all peak area measurements was ≤3.5%. [b] Calculated from the relative isotopic mass spectral ion abundances as described in the Experimental Section. The values in parentheses were calculated from an undiluted sample of [2′,3′,-*N*-CH_3-$^{13}C_3$]nicotine, the *N*-CH_3 of which contained 56–62 mol % excess ^{13}C. [c] Calculated by the methods described in ref 1 from ^{13}C NMR spectrum of the N_b-monoethanesulfonate. [d] Calculated by the method described in the Experimental Section from ^{13}C NMR spectrum of N_b-monoethanesulfonate. [e] Not determined. [f] Calculated from relative peak areas of ^{13}C NMR spectrum of bis(trifluoroacetate). [g] Calculated from relative peak areas of ^{13}C NMR spectrum of free base (pH 8.2). [h] Sample of ~90% [2′,3′,-*N*-CH_3-$^{13}C_3$]nicotine in which the contribution of natural ^{13}C abundance **1b** to I_S was *not* subtracted when calculating the intramolecular ^{13}C enrichment.[1]

The ^{13}C enrichment of one sample of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** containing ~7 mol % excess ^{13}C was determined by mass spectrometry using the *N*-methylpyrrolidinium fragment ion at *m/e* 84 and the fragment ion at *m/e* 133 [$M^+ \cdot$ − C(3′) and C(4′)][45] to measure the ^{13}C enrichment, by ^1H NMR spectroscopy in which the $^1J_{CH}$ and $^2J_{CCH}$ satellite peak areas of a sample of [1′,2′-$^{13}C_2$]-3-acetylpyridine containing ~90 mol % excess ^{13}C were measured, and by ^{13}C NMR spectroscopy using the two methods described in our earlier paper, the *inter*molecular ^{13}C enrichment (total signal area enhancement) and the *intra*molecular ^{13}C enrichment (singlet-to-satellite area ratios corrected for the presence of natural ^{13}C abundance nicotine).[1] The results are shown in Table I(A), in which also is shown (B) the relative ^{13}C enrichment of the triply labeled **1b** calculated by a variation of the original methods (Experimental Section) and of a sample of triply labeled **1b** bis(trifluoroacetate) (C) and free base (D) containing 60–90 mol % excess ^{13}C at the labeled carbons.

The accuracy of our ^{13}C NMR technique for measuring the relative ^{13}C enrichment of **1b** (shown in Table II) is dependent, of course, on what values one chooses as the standard on which the comparison is based. Use of the mass spectral values as the standard is necessary when considering the relative *inter*molecular ^{13}C enrichment, i.e., the total amount of all ^{13}C-labeled molecules present in the sample; here there is

Scheme IV



(• = ^{13}C)

Table II. Relative Error (%) in the Determination of ^{13}C Enrichment of [2′,3′,*N*-CH_3-$^{13}C_3$]Nicotine

	% error of relative ^{13}C enrichment[a]				
	intramolecular		intermolecular		
standard	C(2′)	C(3′)	C(2′)	C(3′)	*N*-CH_3
mass spectrum	−5.8[b,c]	+0.3[c]	−12.1[c]	−17.3[c]	−21.0[c]
	(−1.4)[d]	(−2.2)[d]			
	−4.5[e] (0)	+1.0 (−1.4)	−17.0	−13.9	*f*
^1H NMR	−5.3[b]	+0.2			
	−3.9[e]	+0.9			
^{13}C NMR[g]	+1.0[b]	−3.0			
	−2.4[e]	−2.3			

[a] Refers to data of Table I: A (+) sign indicates the amount the value is greater than the reference value; a (−) sign, the amount the value is less than the reference value. [b] Relative to the values of Table I (A). [c] Based on the mass spectrally determined ^{13}C enrichment of a sample of [2′,3′,*N*-Me-$^{13}C_3$]-**1b** containing ~7 mol % excess ^{13}C at the labeled positions. [d] As in c but using a sample of **1b** *containing 60–90 mol % excess* ^{13}C *at the labeled positions.* [e] Relative to the values of Table I (B). [f] Not determined. [g] Based on the values of Table I (C) as the reference standard.

Table III. T_1 Values for Nicotine N_b-Monoethanesulfonate[a,b]

carbon	T_1,[c] s	T_1,[d] s
C(2)	1.64 ± 0.26	1.54 ± 0.20
C(3)	~6	~6
C(4)	1.41 ± 0.08	1.39 ± 0.08
C(5)	1.39 ± 0.08	1.43 ± 0.10
C(6)	1.12 ± 0.05	1.21 ± 0.07
C(2′)	1.73 ± 0.29	1.97 ± 0.23
C(3′)	0.90 ± 0.14	0.97 ± 0.12
C(4′)	1.23 ± 0.14	1.25 ± 0.11
C(5′)	1.04 ± 0.14	1.16 ± 0.10
N-CH_3	1.11 ± 0.14	1.19 ± 0.10
CH_2[e]	2.74 ± 0.42	2.78 ± 0.34
CH_3[e]	3.40 ± 0.33	3.38 ± 0.37

[a] Determined by the inversion–recovery method using a 1 M solution in D_2O at 37 °C, pH 5.5. [b] These values are significant only as an indication of relative carbon relaxation rates under the same experimental conditions used to obtain relative ^{13}C enrichments of synthetically and biosynthetically ^{13}C-labeled **1b**. [c] Calculated from peak area. [d] Calculated from peak intensity. [e] Carbons of sulfonate anion.

a large apparent error of ±12–21%. This must be due to the inaccuracy in measuring the rather small mass spectral isotopic peak intensities, particularly of the *m/e* 133 fragment ions, of the diluted sample of ^{13}C-labeled **1b**, since good agreement between ^{13}C and ^{14}C derived relative intermolecular isotopic labeling of **1b** was obtained (see Table IV). The best accuracy is obtained when the relative *intra*molecular ^{13}C enrichment is considered, as expected, based on the report of Matwiyoff and Burnham.[6] Again, the largest apparent error was encountered when the mass spectral data from the diluted sample of ^{13}C-labeled **1b** was used as the standard. We note particularly that the values shown in Table I (A–D) are in excellent agreement with the stated relative ^{13}C content of the commercial sample of [1,2-$^{13}C_2$]acetate used in our synthesis: C(1), 91.6 atom %; and C(2), 92.8 atom % ^{13}C.

The accuracy of our quantitative ^{13}C NMR spectroscopic analysis of **1b** also is dependent on the relative spin–lattice relaxation rate of the compound's carbon atoms. When close correspondence between the number of carbons and signal intensity is desired, ^{13}C NMR spectra usually are determined with a long delay time (five or more times a carbon's T_1 value) between successive pulses in the Fourier transform mode, or by the addition of a paramagnetic relaxation reagent.[46] This has been observed to be unnecessary by Matwiyoff and coworkers when the relative intensities of the singlet and satellite resonances of ^{13}C-enriched compounds are being measured under proton noise-decoupling conditions, *if* the carbon in question bears a directly attached proton.[47] Since in our earlier paper the ^{13}C NMR spectra of ^{13}C-labeled **1b** had been determined with an 0.8-s pulse repetition rate, the data recorded in Table I were obtained under similar spectrometer parameters, even though the T_1 values for nicotine's protonated carbons have a range of 0.90–1.97 s when determined on its N_b-monoethanesulfonate salt (Table III). Since the T_1's of the *N*-methylpyrrolidine ring's carbons do not differ greatly under our experimental conditions, it is unlikely that the relaxation of any of these carbons is dominated by processes like spin rotation, which could lead to considerable inaccuracy in the quantitative spectral analysis. Thus such considerations are neglected in analyzing the accuracy of our quantitative ^{13}C NMR analysis of **1b**.

Table IV. Relative Percentage Isotopic Labeling of [^{13}C,^{14}C]-1b after a 240 h Total Metabolism Period[a]

carbon	relative ^{14}C specific radioactivity,[b] %	relative intermolecular ^{13}C enrichment, %
2′	6.7	6.1[c]
5′	6.9	6.8
2 to 6 plus 2′	66	68
2 to 6	59	62

[a] Exposed to $^{13}CO_2$ for 14 h then grown in the normal atmosphere for 226 h. [b] Taken from Table I of ref 5a. [c] Represents percentage of total intermolecular ^{13}C enrichment calculated by subtracting 1.0 from each carbon's value in column 6, Table I, ref 1, and figuring the percentage this value is of the total (13.2).

After considering the above data, it is important to reevaluate the accuracy of our spectral techniques for determining the *inter*molecular ^{13}C enrichment of **1b**. Since this value was defined[1] to represent the total contribution that all ^{13}C-labeled species make to the ^{13}C NMR signal intensity of a given carbon, it can be compared directly to the relative labeling of 1b by carbon-14,[1] whose quantitative analysis can be carried out with high accuracy. Professor Edward Leete has chemically degraded one of our biosynthetically ^{13}C,^{14}C-labeled samples of **1b**[1] by a new method developed in his laboratory. His findings[5a] are summarized in Table IV, from which it can be seen that for carbon 5′ and the carbon sets, C(2) to C(6) plus C(2′), and C(2) to C(6), the accuracy of the ^{13}C NMR technique for quantifying the *relative* intermolecular ^{13}C enrichment of **1b** is good, i.e., within a ±5.1% error range; for carbon 2′ alone, however, the error is larger (−9.0%). Since a ^{14}C reference label was not included during the synthesis of [2′,3′,*N*-Me-$^{13}C_3$]-**1b**, a similar certification of accuracy for the synthetically ^{13}C-labeled **1b** cannot be made. It is our belief, however, that the accuracy of this technique is at least ±10%, better than that shown in Table II, where the accuracy of the mass spectral analysis is too poor to permit much significance to be placed on this part of our results.

Finally, the proton-decoupled ^{13}C NMR spectrum of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** (Figure 1) is clear proof of an assumption we made in our earlier paper: that the mirror image relationship of the satellite resonances for C(2′)/C(3′) and C(4′)/C(5′) was the result of $^1J_{CC}$ coupling in these pairs of carbons, which form AB spectral subsets.[48] This relationship of satellite intensities is well known in proton NMR spectroscopy, but it has particular value in the present study for easy identification of some ^{13}C labeling relationships in the complex mixture of multiply ^{13}C-labeled molecules when recourse to ^{13}C–^{13}C

homonuclear decoupling techniques is not available. Consequently, it now is certain that the second-order $^1J_{CC}$ relationships are evidence for the biosynthetic origin of these two-carbon sets from biochemical C_2 units. This conclusion is consistent with the expected flow of carbon-13 via acetic acid through the tricarboxylic acid cycle and the labeling of the *N*-methylpyrrolidine ring of **1b** by [^{14}C]acetate reported several years ago by Zielke and Byerrum.[49]

Conclusions

The development of an efficient synthesis of **1a** and **1b**, which was used to prepare a sample of (±)-[2′,3′,*N*-Me-$^{13}C_3$]nicotine, has permitted us to certify that the accuracy of the ^{13}C NMR techniques used to determine the relative ^{13}C enrichment of nicotine, biosynthetically labeled by $^{13}CO_2$, is sufficient to validate part of the data presented in our initial paper.[1] That is, that the difference in the relative *intra*molecular ^{13}C labeling of the C(2′)/C(3′) and C(4′)/C(5′) two-carbon units of **1b** (8–21%) is larger than the experimental error, determined in this study to be ≤±6%. On the other hand, the apparent differences in the *inter*molecular ^{13}C enrichment of **1b** reported earlier are less than the experimental error determined in this study, and are unlikely to be significant.

It is tempting to propose a biochemical explanation of our results at this time, which others find puzzling.[5b] However, *since only one biosynthetically ^{13}C-labeled sample of* **1b** *was measured,*[1] *we feel it is too early to determine what significance this has to nicotine biosynthesis.* Yet we believe that it is quite possible to encounter equal intermolecular ^{13}C labeling via biochemical passage of carbon-13 through a symmetrical intermediate, e.g., **2**, but to encounter unequal intramolecular ^{13}C labeling of a carbon subset of the same intermediate, since the latter's intramolecular ^{13}C labeling can be "symmetrized" only by a bond breakage and statistically random recombination of the two coupled carbon atoms. There simply is not any basis at present to assume that as a result of the metabolic processes which join the two carbons (from $^{13}CO_2$ in our case) that ultimately form C(4′) and C(5′) of **1b**, these carbons will be equally intramolecularly ^{13}C labeled. Hopefully in future work we are planning the results obtained will permit us to shed some light on this question.

Experimental Section

General. Reagents and organic chemicals were of commercial quality. The 90% sodium[1,2-$^{13}C_2$]acetate was purchased from Merck and Co. and the 90% [^{13}C]formaldehyde from Stohler Isotopes. Solvents were redistilled and THF was distilled from $LiAlH_4$ immediately before its use. Oxygen-free nitrogen was obtained through use of a deoxygenation catalyst (BASF R-33). Thick-layer (PLC), thin layer (TLC), and column chromatography were done using the appropriate Brinkmann silica gel. Infrared spectra were determined on a Perkin-Elmer 237 grating spectrophotometer. Mass spectra were run on an AEI MS-9 interfaced to a Nova 2 computer or a Finnegan quadrupole 1015 GC/mass spectrometer interfaced to a Finnegan M6000 computer. Nuclear magnetic resonance spectra were determined at 90 MHz (^{1}H) on a Bruker HX-90E or Varian EM 390 spectrometer, at 22.63 MHz (^{13}C) on a Bruker HX-90E using the parameters described under each figure, or those reported earlier.[1]

2,2-Bis(ethylthio)ethanal. To 1,1-bis(ethylthio)methane (10.88 g, 0.08 mol) in dry tetrahydrofuran (160 mL) magnetically stirred at −30 °C under a nitrogen atmosphere was added *n*-butyllithium (35.2 mL, 2.5 M, 0.088 mol) as a hexane solution. After 1 h additional stirring, the resulting dithioalkyllithium was transferred into previously cooled (−10 °C) dry dimethylformamide (24 mL) by a cannula using a slight positive nitrogen pressure. The reaction mixture was kept at −10 °C overnight, then poured into ice water (150 mL). The basic aqueous solution was extracted with Skellysolve A (3 × 150 mL), followed by acidification with 3 N hydrochloric acid to pH 6, and extracted with diethyl ether (3 × 150 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The product was purified by distillation to give 11.86 g (91%) of a colorless liquid: bp 67 °C (0.3 Torr); IR (neat) ν 2708, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.20 (d, *J* = 4.2 Hz, 1 H), 4.25 (d, *J* = 4.2 Hz, 1 H), 2.63 (q, *J* = 7.4 Hz, 4 H), and 1.27 (t, *J* = 7.4 Hz, 6 H). Anal. ($C_5H_{12}S_2O$) C, H, S.

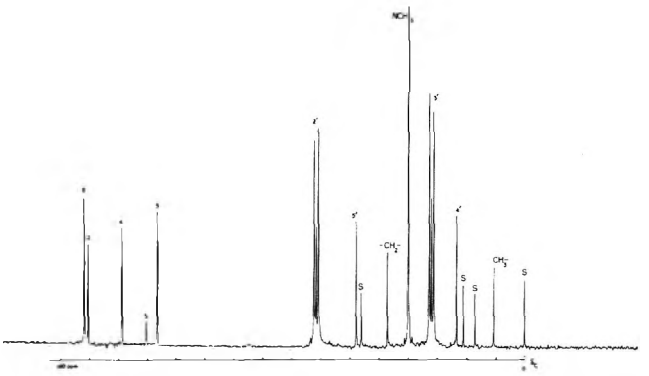


Figure 1. Proton-decoupled ^{13}C NMR spectrum of the monoethanesulfonate salt of [2′,3′,*N*-CH_3-$^{13}C_3$]nicotine (**1b**), ~0.3 M, in D_2O. The resonances marked *S* are of the DSS internal standard and signal assignments are taken from ref 1 as recently confirmed by T. P. Pitner, J. I. Seeman, and J. F. Whidby, *J. Heterocycl. Chem.*, in press.

2-Formyl-1,3-dithiane. Prepared from 1,3-dithiane as above to give a colorless liquid in 81% yield: bp 93 °C (0.8 Torr) [lit.[50] 83–85 °C (0.45 Torr)]; IR (neat) ν 2700, 1715, 910 cm^{-1}.

1-Acetyl-2,2-bis(ethylthio)ethanol. To 2,2-bis(ethylthio)ethanal (11.85 g, 0.072 mol) in ethanol (110 mL) was added sodium borohydride (1.5 g, 0.039 mol) in several portions while magnetically stirring at 25 °C. The reaction mixture was stirred overnight and acidified with 3 N hydrochloric acid to pH 5–6, and the ethanol was mostly removed by evaporation in vacuo. The resulting material was extracted with diethyl ether (3 × 200 mL) and the combined ether extracts were dried over anhydrous magnesium sulfate. The crude alcohol, obtained as a colorless liquid upon removal of the solvent in vacuo, was acetylated at 25 °C using acetic anhydride (1.5 mL) and pyridine (5 mL). Excess acetic anhydride was destroyed by an addition of water (1 mL) to the reaction mixture and acidification with 3 N hydrochloric acid to pH 1. The resulting solution was extracted with diethyl ether (3 × 200 mL), the combined ether extracts were washed with saturated aqueous sodium bicarbonate and brine, and the ether solution was dried over anhydrous magnesium sulfate. Removal of ether in vacuo followed by distillation gave a colorless liquid (13.51 g, 91%): bp 87 °C (0.3 Torr); IR (neat) ν 1750, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.5–3.8 (m, 3 H), 2.70 (q, *J* = 7.8 Hz, 4 H), 2.10 (s, 3 H), and 1.27 (t, *J* = 7.8 Hz, 6 H). Anal. ($C_8H_{16}S_2O_2$) C, H, S.

2-Acetoxymethyl-1,3-dithiane. Prepared from 2-formyl-1,3-dithiane as above to give the intermediate alcohol as a colorless crystalline solid in 95% yield: mp 35.0–35.8 °C (from dichloromethane/Skellysolve A (1:3)); IR (KBr) ν 3400, 1069, 908 cm^{-1}. Anal. ($C_5H_{10}OS_2$) C, H, S. Its acetate was prepared as above to give a colorless liquid in 94% yield: bp 110–111 °C (1.5–2 Torr); IR (neat) ν 1745, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.5–3.9 (m, 3 H), 3.2–2.5 (m, 4 H), 2.08 (s, 3 H), and 2.3–1.9 (m, 2H). Anal. ($C_7H_{12}O_2S_2$) C, H, S.

Ketene Thioacetal Monoxide 4. To 1-acetyl-2,2-bis(ethylthio)-ethanol (13.4 g, 0.0644 mol) dissolved in methanol (90 mL) and water (28 mL) was added sodium metaperiodate (13.8 g, 0.0644 mol) in 3-g portions over 15-min intervals at 0 °C with vigorous stirring. Stirring was continued at 22 °C for 24 h, whereupon the white solid precipitate was separated by filtration and the filter cake was washed with diethyl ether (100 mL). The volume of the combined ether/aqueous methanol filtrate was reduced to ~100 mL. The filter cake was triturated with dichloromethane (200 mL) and this organic filtrate was combined with the former. The resulting two-phase solution was extracted with dichloromethane (3 × 150 mL) and the resulting combined dichloromethane extracts were washed with 10% aqueous sodium bisulfite (50 mL) and then saturated aqueous sodium carbonate. The solution was dried over anhydrous magnesium sulfate and evaporated in vacuo to give the monosulfoxide acetate as a colorless liquid (14.0 g).

To a vigorously stirred solution of the monosulfoxide acetate (14.0 g, 0.063 mol) dissolved in benzene (63 mL) was added powdered potassium hydroxide (7.1 g, 0.126 mol) and anhydrous potassium carbonate (17.4 g, 0.126 mol). The reaction mixture was stirred at 22 °C for 3 h, whereupon dichloromethane (100 mL) and Celite (5–10 g) were added and the resulting mixture was then filtered under vacuum through anhydrous magnesium sulfate. Evaporation of the solvent gave a residual oil, which on distillation afforded pure **4** (8.8 g, 84%): bp 62 °C (0.38 Torr); IR (neat) ν 3095, 1750, 1060 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 6.30 (d, J = 1 Hz, 1 H), 5.96 (d, J = 1 Hz, 1 H), 2.87 (m, 4 H), and 1.20 (m, 6 H). Anal. ($C_6H_{12}OS_2$) C, H, S.

Ketene Thioacetal Monoxide 6. Prepared from 2-acetoxymethyl-1,3-dithiane as above, giving **6** as a colorless solid in 82% yield (two steps): mp 44.7–45.1 °C; bp 98 °C (0.3 Torr); IR (neat) ν 3090, 1747, 1055, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.14 (s, 1 H), 6.28 (s, 1 H), 3.6–3.2 (m, 1 H), and 3.0–2.2 (m, 5 H). Anal. ($C_5H_8OS_2$) C, H, S.

δ-Keto Sulfoxide 5. 3-Acetylpyridine (234 mg, 1.93 mmol) was added dropwise to lithium diisopropylamide (LDA, 2.25 mmol) in THF (5 mL) at −78 °C under an N_2 atmosphere. The resulting solution was warmed to −5 °C for 30 min and cooled to −78 °C, and **4** (298 μL, 2.0 mmol) was added dropwise with magnetic stirring. The reaction was stirred at −10 °C for 19 h then worked up by addition of water (1 mL) followed by acidification with 2 N HCl (10 mL). The acidified aqueous solution was extracted with EtOAc (2 × 20 mL), and then an acidic (2 N HCl, 10 mL) backwash of the EtOAc layer was combined with the first acidic aqueous layer, which was basified with concentrated NH_4OH and saturated with solid NaCl. Extraction of the resulting aqueous solution with EtOAc (3 × 50 mL), drying of the combined organic extracts (Na_2SO_4), and solvent removal in vacuo gave a crude viscous gum. This residue was purified by PLC in $CHCl_3$/MeOH/NH_4OH (180:20:1) and the major UV absorbing product was eluted with CH_2Cl_2/MeOH (4:1) to give **5** after solvent removal in vacuo as a viscous oil (215 mg, 37.7%): IR (neat) ν 1700, 1600, 1460, 1430, 1390, 1280, 1060, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.22 (d, J = 2.0 Hz, 1 H), 8.82 (dd, J = 1.6, 4.8 Hz, 1 H), 8.29 (dt, J = 1.7, 8.0 Hz, 1 H), 7.46 (dd, J = 4.8, 8.0 Hz, 1 H), 4.03–3.63 (m, 1 H), 3.60–1.80 (m, 8 H), and 1.33 (pseudo q, J = 7.6 Hz, 6 H); MS *m/e* (rel intensity) 207 ($M^{+\cdot}$ − $HOSC_2H_5$, 62) [$C_{11}H_{13}NOS$ calcd 207.0698, found 207.0708], 152 (4), 146 (51), 118 (30), 117 (12), 106 (100), 101 (20), 92 (4), 91 (5), 78 (75).

δ-Keto Sulfoxide 7. 3-Acetylpyridine (244 mg, 2 mmol) was slowly added to LDA (2 mmol) in THF (4 mL) at −78 °C with magnetic stirring under an N_2 atmosphere. After 30 min, **6** (296 mg, 2 mmol) was added dropwise. The reaction was stirred at − 78 °C for 2 h, at −10 °C for 4.5 h, then at 25 °C for 15 h. Workup as for **5** gave **7** (246 mg, 45.5%) as a colorless oil: IR ($CHCl_3$) ν 1690, 1590, 1483, 1421, 1368, 1315, 1235, 1030, 790, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.35 (br s, 1 H), 8.96 (dd, J = 1.9, 4.8 Hz, 1 H), 8.44 (dt, J = 1.9, 8.3 Hz, 1 H), 7.62 (dd, J = 4.8, 8.3 Hz, 1 H), 3.98 (dd, J = 5.2, 7.6 Hz, 1 H), 3.50 (br t, J = 6 Hz, 2 H), and 3.3–1.8 (m, 8 H); MS *m/e* (rel intensity) 269 (M^+, 17) [$C_{12}H_{15}NO_2S_2$ calcd 269.0538, found 269.0541], 146 (72), 121 (14), 118 (19), 106 (95), 91 (34), 87 (44), 79 (41), 78 (100).

3-Acetylpyridine Methoxime 11. Powdered NaOH (3.20 g, 80 mmol) was added to a magnetically stirred solution of 3-acetylpyridine (2.2 g, 20 mmol) and methoxyamine hydrochloride (2.5 g, 30 mmol) in 95% ethanol (14 mL)–water (3 mL). After a 5-min reflux of the reaction the mixture was saturated with solid NH_4Cl and NaCl, and the products were extracted with EtOAc (5 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and distilled to give **11** (2.98 g, 99%): bp 114 °C (25 mmHg); IR (neat) ν 1615, 1590, 1568, 1055, 900, and 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.84 (d, J = 1.5 Hz, 0.87 H), 8.73 (d, J = 1.5 Hz, 0.13 H), 8.55 (dd, J = 1.5, 5.1 Hz, 1 H), 7.93 (dt, J = 1.5, 7.8 Hz, 0.87 H), 7.82 (dt, J = 1.5, 7.8 Hz, 0.13 H), 7.24 (dd, J = 5.1, 7.8 Hz, 1 H), 3.98 (s, 2.67 H), 3.84 (s, 0.33 H), and 2.19 (s, 3 H); ^{13}C NMR δ ($CDCl_3$) (rel signal area) 11.87 (6.5), 20.82 (1.8), 62.03 (10.6), 61.66 (2.0), 123.20 (17.9), 132.97 (16.4), 135.50 (15.4), 147.53 (17.1), 149.31 (2.3), 150.01 (24.9), and 151.85 (1.6); MS *m/e* (rel intensity) 150, $M^{+\cdot}$, 100) [$C_8H_{10}H_2O$ calcd 150.0793, found 150.0786], 119 (20), 112 (47), 104 (20), 78 (97).

Methoxime Sulfoxide 12a. Methoxime **11** (2.25 g, 15 mmol) was added to LDA (16.5 mmol) in THF (30 mL) at −78 °C under an N_2 atmosphere with magnetic stirring. After 20 min **4** (2.23 mL, 15 mmol) was added to the yellow solution and stirring was continued for 3 h at −78 °C. The reaction was quenched at −78 °C by the addition of H_2O and solid NH_4Cl. After warming and saturation with NaCl the reaction mixture was extracted with EtOAc (4 × 100 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting residue was purified by column chromatography in ether to give **12a** (4.1 g, 86%) as a colorless oil: IR (neat) ν 1650, 1585, 1565, 1450, 1410, 1050, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.90 (d, J = 2.1 Hz, 1 H), 8.58 (dd, J = 2.1, 5.1 Hz, 1 H), 7.97 (dt, J = 8.4, 2.1 Hz, 1 H), 7.28 (dd, J = 5.1, 8.4 Hz, 1 H), 3.99 (s, 3 H), 3.72–3.45 (m, 1 H), 3.22–2.23 (m, 8 H), 1.35 (t, J = 7.5 Hz, 3 H), and 1.33 (t, J = 7.5 Hz, 3 H); MS *m/e* (rel intensity) 237 (34), 206 (4), 175 (38), 162 (3), 161 (3), 160 (3), 145 (14), 144 (12), 131 (5), 118 (8), 117 (6), 106 (16), 101 (100). Anal. ($C_{14}H_{22}N_2O_2S_2$) C, H, N, S.

4-Amino Thioacetal 13. Methoxime sulfoxide **12a** (1.74 g, 5.54 mmol) was cooled to ice bath temperatures with magnetic stirring and diborane (1 M solution in THF, 38.8 mL) was added. The reaction was stirred 10 min, allowed to warm to room temperature and kept there for 12–16 h, and then refluxed for 3.5 h. After cooling to room temperature excess B_2H_6 was destroyed by the addition of MeOH and the reaction was stirred for 12–16 h. After solvent removal in vacuo the residue was treated with 10% NaOH (38 mL) and the resulting solution was refluxed for 1 h. After cooling to room temperature the reaction mixture was neutralized with solid NH_4Cl, saturated with KCl, and extracted with EtOAc (6 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give **13** as a colorless liquid (1.50 g, 100%), pure by ^1H NMR analysis: IR (neat) ν 3370, 3280, 1595, 1580, 1450, 1425, 1265, 1170, 1025, 915, and 717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62–8.43 (m, 2 H), 7.72 (dt, J = 7.8, 1.5 Hz, 1 H), 7.24 (dd, J = 4.8, 7.8 Hz, 1 H), 3.98 (t, J = 6.0 Hz, 1 H), 3.76 (t, J = 6.6 Hz, 1 H), 2.60 (q, J = 7.2 Hz, 1 H), 2.57 (q, J = 7.2 Hz, 1 H), 2.15–1.60 (m, 4 H), and 1.21 (t, J = 7.2 Hz, 6 H); MS *m/e* (rel intensity) 270 (M^+, 23) [$C_{13}H_{22}N_2S_2$ calcd 270.1225, found 270.1229], 241 (35), 224 (55), 210 (16), 208 (33), 192 (74), 147 (31), 146 (11), 131 (12), 130 (74), 121 (16), 120 (100), 107 (56), 105 (11).

Isomyosmine (10). Iodine (88 mg, 0.35 mmol) was added to magnetically stirred **13** (92 mg, 0.34 mmol) dissolved in CH_3CN/H_2O (3:1) at room temperature. After 1 h, AgOAc (56 mg, 0.34 mmol) was added and the reaction again was treated with the same amount of iodine then AgOAc, followed by filtration to remove precipitated solids. The filtrate was decolorized by addition of 10% aqueous $Na_2S_2O_3$, basified with saturated aqueous $NaHCO_3$, and continuously extracted with CH_2Cl_2 for 48 h. After drying the CH_2Cl_2 extract (Na_2SO_4) and evaporation in vacuo, the resulting oil was purified by PLC as for **5** to give **10**[51] (20.5 mg, 41%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.60–8.43 (m, 2 H), 7.83 (br s, 1 H), 7.55 (dt, J = 1.5, 7.8 Hz, 1 H), 7.24 (dd, J = 4.5, 7.8 Hz, 1 H), 5.12 (t, J = 8.1 Hz, 1 H), and 2.90–2.17 (m, 4 H); MS *m/e* (rel intensity) 146 (M^+, 3), 145 (8), 118 (100), 105 (7), 104 (5), 91 (35).

Reduction of **10** (51.5 mg, 0.35 mmol) with $NaBH_4$ according to a literature method[7i] gave **1a** (34 mg, 66%) identified by TLC comparison with an authentic reference standard.

Hydrolysis of **13** (360 mg, 1.33 mmol) in glacial AcOH (13 mL) using iodine (1.65 g, 6.65 mmol) for 1 h followed by reduction of excess I_2 with aqueous 10% $Na_2S_2O_3$, addition of NaOAc (6.65 mmol), evaporation of the solvent, pH adjustment to 7–8 with aqueous $NaHCO_3$, addition of solid NaOH (110 mg) in MeOH (13 mL), and reduction using $NaBH_4$ (48 mg) gave **1a** (0.46 mmol, 35%) after the workup described above. The yield of **1a** (30–40%) varied seemingly dependent on the purity of **13**.

N_b-Formylnornicotine (14). The crude 4-amino thioacetal **13** (105 mg, 0.39 mmol) was refluxed in 97% HCOOH (1.5 mL) for 3 h. The reaction mixture was concentrated in vacuo at <30 °C and treated with a few drops of saturated aqueous $NaHCO_3$ followed by solid Na_2SO_4. The resulting semisolid mass was extracted with EtOAc (5 × 50 mL) until no more UV-absorbing material was detectable. The combined EtOAc extracts were concentrated in vacuo and purified by PLC as for **5** to give **14**[52] (53 mg, 75%) as a pale yellow oil: IR (neat) ν 2875, 1665, 1580, 1425, 1380, 1025, and 718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.63–8.40 (m, 2 H), 8.37 (s, 0.4 H), 8.10 (s, 0.6 H), 7.53 (m, 1 H), 7.25 (m, 1 H), 5.18–4.85 (m, 1 H), 3.76–3.55 (m, 2 H), 2.56–2.25 (m, 1 H), and 2.15–1.83 (m, 1 H); MS *m/e* (rel intensity) 176 (M^+, 100) [$C_{10}H_{12}N_2O$ calcd 176.0950, found 176.0950], 147 (57), 120 (21), 119 (36), 118 (17).

Nornicotine (1a). *N*-Formylnornicotine (19 mg, 0.11 mmol) was refluxed with 3 N HCl (7.2 mL) for 2 h. The reaction was basified with saturated aqueous $NaHCO_3$ and continuously extracted with CH_2Cl_2 for 48 h. Final purification as described for **5** gave the dihydrochloride salt of **1a** (22 mg, 0.1 mmol, 92%) identified by TLC and NMR of its free base vs. authentic **1a**.

Nicotine (1b) *N*-Formylnornicotine (21 mg, 0.12 mmol) in 97% HCOOH (0.5 mL) and 37% formalin (0.5 mL) was heated in a sealed tube at 100 °C for 18 h. The reaction mixture was evaporated in vacuo at <30 °C, 2 drops of H_2O and solid $NaHCO_3$ were added, and the resulting solid mass was extracted with Et_2O (5 × 2 mL). The combined ether extracts were concentrated in vacuo at 0–10 °C and purified by PLC as with **5** to give the dihydrochloride salt of **1b** (26 mg, 93%), identified by TLC and NMR of its free base vs. authentic **1b**.

This alkaloid (45 mg, dihydrochloride) also was obtained directly from **13** (75 mg) in 68% overall yield without isolation of intermediate products; the overall yield of one other preparation was 81%.

Mesylates 17 and 18. 3-Acetylpyridine (230 μL, 2.1 mmol) was added to a magnetically stirred suspension of Skellysolve A washed NaH (2.1 mmol) in DMF (5 mL) under an N_2 atmosphere and stirred for 2 h at 0 °C. Mesylaziridine[31] **16** (242 mg, 2 mmol) in DMF (2 mL) was added slowly and the reaction mixture was stirred for 5 h at 0 °C. The reaction was quenched by addition of NH_4Cl (1 g) in H_2O (10 mL)

followed by saturation of the solution with NaCl and extraction with EtOAc (5 × 40 mL). The combined organic extracts were dried ($MgSO_4$), the solvents were removed in vacuo, and the resulting residue was purified by PLC as for **5**. Compound **17** (100 mg, 21%) was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.83 (br s, 1 H), 8.50 (d, J = 4.5 Hz, 1 H), 7.87 (dt, J = 1.5, 7.8 Hz, 1 H), 7.24 (dd, J = 4.5, 7.8 Hz, 1 H), 4.74 (d, J = 3.0 Hz, 1 H), 4.34 (d, J = 3.0 Hz, 1 H), 4.02 (t, J = 4.8 Hz, 2 H), 3.56 (t, J = 4.8 Hz, 2 H), and 2.97 (s, 3 H).

Compound **18** (91 mg, 19%) also was obtained as a colorless oil: ^1H NMR (Me_2SO-d_6) δ 9.10 (d, J = 1.5 Hz, 1 H), 8.78 (dd, J = 1.5, 4.8 Hz, 1 H), 8.28 (dt, J = 1.5, 7.8 Hz, 1 H), 7.56 (dd, J = 4.8, 7.8 Hz, 1 H), 3.26–2.94 (m, 4 H), 2.88 (s, 3 H), and 1.82 (q, J = 6.9 Hz, 2 H); MS *m/e* (rel intensity) 242 (M^+) [$C_{10}H_{14}N_2O_3S$ calcd 242.0775, found 242.0750] 163 (71), 146 (15), 134 (9), 122 (35), 121 (27), 106 (100), 79 (40), 78 (79).

Myosmine (3) and N_b-Mesylmyosmine (19). The C-alkylated mesylate **18** (82 mg, 0.34 mmol) was refluxed in toluene (10 mL) containing *p*-toluenesulfonic acid hydrate (65 mg, 0.34 mmol) for 3 h in an apparatus set up to permit the condensing toluene to pass through Linde 4A molecular sieves. The reaction was basified to pH 10 with 10% aqueous NaOH, solid NaCl was added to saturation, and the mixture was extracted with EtOAc (5 × 50 mL). The combined organic extracts were dried (Na_2SO_4), the solvents were removed in vacuo and the resulting residue was purified by PLC as for **5**. Two major products were isolated as colorless oils.

N_b-Mesylmyosmine (**19**; 20 mg, 26%): ^1H NMR ($CDCl_3$) δ 8.73 (br s, 1 H), 8.57 (d, J = 4.8 Hz, 1 H), 7.58 (dt, J = 1.5, 7.8 Hz, 1 H), 7.21 (dd, J = 4.8, 7.8 Hz, 1 H), 5.73 (t, J = 7.8, 1 H), 4.11 (t, J = 8.1 Hz, 2 H), 2.81 (s, 3 H), and 2.70 (dt, J = 2.8, 8.1 Hz, 2 H); MS *m/e* (rel intensity) 224 (M^+, 41), 161 (4), 145 (100), 144 (37), 118 (45), 117 (74), 105 (25), 92 (22), 91 (22), 90 (12), 89 (16), 79 (10), 78 (15).

Myosmine (**3**;[7i] 8 mg, 15%): ^1H NMR ($CDCl_3$) δ 9.00 (d, J = 1.5 Hz, 1 H), 8.65 (dd, J = 1.5, 4.8 Hz, 1 H), 8.21 (dt, J = 1.5, 8.1 Hz, 1 H), 7.36 (dd, J = 4.8, 8.1 Hz, 1 H), 4.12 (m, 2 H), 2.98 (m, 2 H), and 2.11 (m, 2 H); MS *m/e* (rel intensity) 146 (M^+, 50), 145 (45), 118 (100), 105 (21), 91 (16), 78 (34).

Reduction of **3** with $NaBH_4$ as for **10** gave the dihydrochloride salt of **1a** (8 mg, 66%), identified as before.

[1′,2′-$^{13}C_2$]-3-Acetylpyridine. A typical experiment for the unlabeled synthesis is presented followed by the yields obtained in the ^{13}C-labeled synthesis.

A magnetically stirred suspension of NaOAc (1.23 g, 15 mmol) in THF (5 mL) contained in a heavy-walled tube fitted with a pressure stopcock was treated with concentrated H_2SO_4 (450 μL). The mixture was cooled to 0 °C, diborane in THF (1 M, 18 mL) was added, and the reaction mixture was stirred for 1 h at 0 °C then overnight at room temperature. The THF was removed in vacuo under anhydrous conditions and NaOH (0.8 g) in H_2O (4 mL) was added to decompose the boroxine. The resulting mixture was frozen in liquid N_2 and evacuated on a high vacuum line to 5 × 10^{-3} Torr. The mixture of water and ethanol thus was vacuum transferred into a heavy-walled tube, the upper one-half of which was jacketed with a cold-water condenser, containing I_2 (6.8 g) and red phosphorus (0.67 g), and the resulting mixture was heated in a steam bath for 2 h. The reaction tube was frozen in liquid N_2 and the contents was vacuum transferred into a tube containing solid Na_2CO_3 (5 g). After CO_2 evolution had ceased, the ethyl iodide was purified by vacuum transfer through solid NaOH into P_2O_5 (10 g) and the resulting mixture was warmed, frozen, and then vacuum transferred through Linde 4A molecular sieves to obtain a colorless liquid (1.52 g, 65%).

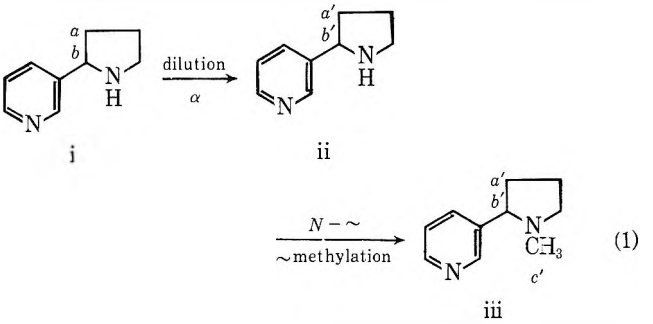
3-Bromopyridine (250 μL, 2.5 mmol) was slowly added to magnetically stirred *n*-butyllithium (2.0 M, 1.25 mL) in THF (10 mL) at −95 °C (liquid N_2–toluene mixture). After 30 min ethyl iodide (82 μL, 1 mmol) was added dropwise to the brown solution of 3-lithiopyridine and stirring was continued for 3 h at −95 °C. The cold reaction was quenched by addition of H_2O, acidified with 6 N HCl (10 mL), and extracted with Et_2O (2 × 25 mL) to remove *n*-butyl bromide. The acidic aqueous layer was basified with solid $NaHCO_3$, saturated with KCl, and extracted with Et_2O (5 × 25 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated in vacuo at <0 °C, and the residue was purified by PLC as for **5**. The hydrochloride salt of 3-ethylpyridine (110 mg, 77%) thus was obtained as a white solid; it was identified by TLC and NMR comparison (free base) with an authentic reference standard.

3-Ethylypridine (86 mg, 0.8 mmol) was mixed with MgO (160 mg, 4 mmol), H_2O (4 mL), $KMnO_4$ (632 mg, 4 mmol), and concentrated HNO_3 (0.54 mL, 8.2 mmol), and the mixture was stirred 5 h at room temperature. Aqueous 10% $Na_2S_2O_3$ was added to reduce the excess $KMnO_4$, the precipitated MnO_2 was filtered off and washed with 2% aqueous HCl (3 × 3 mL), and the combined filtrates were basified ($NaHCO_3$), saturated with NaCl, and extracted with EtOAc (4 × 20 mL). After addition of 2% aqueous HCl (10 mL), the combined organic layers were evaporated in vacuo to give pure 3-acetylpyridine (89 mg, 71%) as its hydrochloride salt. When pyridine (fivefold excess relative to 3-ethylpyridine) also was added to the oxidation reaction mixture, the yield of 3-acetylpyridine increased to 83% after PLC purification.

The following yields were obtained during the ^{13}C-labeled preparation starting with 90% sodium [1,3-$^{13}C_2$]acetate (1 g, 12 mmol): [1,2-$^{13}C_2$]ethyl iodide (0.9 g, 48%); [1′,2′-$^{13}C_2$]-3-acetylpyridine methoxime (201 mg, 23%). The lower yield of ethyl iodide obtained here was the result of inadventitious bumping during the THF removal after boroxine formation.

[2′,3′,*N*-CH_3-$^{13}C_3$]Nicotine. The [1′2′-$^{13}C_2$]-3-acetylpyridine methoxime was converted into **12a** (307 mg, 73%), which was divided into three portions. The first portion (135 mg) was lost when the conversion of **13** into **1a** using I_2/AcOH and $NaBH_4$ failed. The second portion (18 mg) was diluted (~4.8-fold) with unlabeled **12a** (68 mg) and gave [1′,2′-$^{13}C_2$]-**13** (75 mg, 100%). This was converted into the dihydrochloride salt of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** (45 mg, 69%) using ~15 atom % [^{13}C]formaldehyde. The third portion (154 mg) was converted without dilution into ~90% [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** dihydrochloride (7 mg, 6%), the reason for the low overall yield being unaccountable.

Mass Spectral Analysis of [2′,3′,*N*-CH_3-$^{13}C_3$]-1b. The following method was used to calculate the intermolecular and intramolecular ^{13}C labeling shown in Table I of the text. Let eq 1 represent the operations carried out in the preparation of the diluted sample of ^{13}C-labeled **1a** where α is a dilution coefficient and a, b, a', b', and c' are ^{13}C labeling probabilities such that $a = \alpha a'$ and $b = \alpha b'$ by definition. The diluted, triply ^{13}C-labeled **1b** is represented by iii.



Since the fragment ion at *m/e* 84 contains a', b', and c', the intensity of the *m/e* 85 fragment ion contains contributions which can be expressed by $[a(1-b)(1-c')/\alpha] + [b(1-a)(1-c')/\alpha] + c'[1 - \{[a(1-b)/\alpha] + [b(1-a)/\alpha] + [ab/\alpha]\}]$, of the *m/e* 86 fragment ion by $[ab(1-c')/\alpha] + [a(1-b)c'/\alpha] + [b(1-a)c'/\alpha]$, and of the *m/e* 87 fragment ion by abc'/α. Thus by simplification of the contributions, the intensity of the *m/e* 85 fragment ion can be expressed as $a' - b' + c' - 2a'b'\alpha - 2a'c' - 2b'c' + a'b'c'\alpha$, of the *m/e* 86 fragment ion as $a'b'\alpha + a'c' + b'c' - 3a'b'c'\alpha$, and of the *m/e* 87 fragment ion as $a'b'c'\alpha$. Since the mass spectrum of the diluted sample of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** did not exhibit an *m/e* 87 fragment ion of significant intensity, a further approximation of these ion intensity expressions can be made: the *m/e* 85 fragment ion's intensity can now be approximated by $a' + b' + c' - 2a'b'\alpha$], and the *m/e* 86 fragment ion's by $a'b'\alpha$. The measured mass spectral ion intensities were

	unlabeled **1b**		^{13}C-labeled **1b**		
m/e	85	86	85	86	87
intensity	5.5 ± 0.18	0.09 ± 0.02	12.14 ± 0.38	6.48 ± 0.19	0.18 ± 0.03

from which the corrected relative intensity of the *m/e* 85 fragment ion (5.83%) and the *m/e* 86 fragment ion (5.35%), relative to the intensity of the *m/e* 84 fragment ion, were calculated.

Using a similar development the intensity of the *m/e* 134 fragment ion, which contains isotopic contributions from C(2′) and *N*-CH_3 of **1b**, can be expressed as $b'(1-c') + c'(1-b')$, which simplified to $b' + c' - 2b'c'$, and of the *m/e* 135 fragment ion, $b'c'$. Since again the intensity of the *m/e* 135 fragment ion was insignificant in the mass spectrum of the diluted sample of [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b**, the *m/e* 134 fragment ion's intensity is approximated by $b' + c'$. The measured mass spectral ion intensities were

	unlabeled **1b**		^{13}C-labeled **1b**	
m/e	134	135	134	135
intensity	11.68 ± 0.78	0.46 ± 0.22	23.14 ± 0.69	0.74

from which the corrected relative intensity of the m/e 134 fragment ion (10.28%) was calculated. Thus, $a' + b' + c' - 2a'b'\alpha = 5.83 \times 10^{-2}$, $a'b'\alpha = 5.35 \times 10^{-2}$, and $b' + c' = 10.28 \times 10^{-2}$, from which it calculates that $a' = 7.14 \times 10^{-2}$.

From the original definitions of a and b, and from the ^{13}C labeling probabilities shown in Table I(C) for C(2′) and C(3′), it calculates that $a = 93.1$, $b = 85.6$, $a' = 6.25$, $b' = 5.75$, and $c' = 4.53$, each value $\times 10^{-2}$, when α is calculated from the ^1H NMR derived values for C(2′) and C(3′) relative ^{13}C enrichment shown in Table I.

^{13}C NMR Analysis of [2′,3′,*N*-CH_3-$^{13}C_3$]-1b. (a) The values shown in Table I(A) were calculated according to footnote c of Table I and eq 4 of ref 1 from the following relative peak area weights (milligrams) of the ^{13}C NMR resonances:

unlabeled monoethanesulfonate of **1b**

-CH_2-	C(3′)	C(2′)	*N*-CH_3
13.40 ± 0.27 (1)	22.78 ± 0.73 (1.70)	23.78 ± 0.56 (1.78)	21.37 ± 0.06 (1.59)

^{13}C-labeled monoethanesulfonate of **1b**

	C(3′)		C(2′)		
-CH_2-	I_S	I_D	I_S	I_D	*N*-CH_3
5.72 ± 0.20	15.78 ± 0.58	60.31 ± 1.19	14.56 ± 0.15	56.66 ± 1.44	56.55 ± 0.74

For example, for the intramolecular ^{13}C labeling proabability of C(2′)

$$I_{S_{3'}} = 15.78 - (5.72 \times 1.70) = 6.06$$

$$P_{2'} = \frac{60.31}{6.06 + 60.31} = 0.9087$$

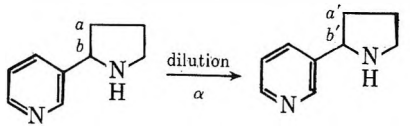
and for the intermolecular ^{13}C labeling of C(2′)

$$I_{S_{2'}} = 14.59 - (5.72 \times 1.78) = 4.41$$

$$\text{total signal intensity} = 56.66 + 4.41 = 61.07$$

$$\%\ ^{13}C \text{ enrichment} = \frac{61.07 \times 1.1\%}{(5.72 \times 1.78)} = 6.60\%.$$

(b) The values shown in Table I(B) were calculated according to the following method. Let eq 2 represent the operations carried out



(2)

in preparing the diluted sample of [2′,3′-$^{13}C_2$]-**1a**, where a, b, a', and b' are the appropriate ^{13}C labeling probabilities of C(3′) and C(2′) of **1b** (or **1a**). Also let c represent the ^{13}C labeling probability of natural abundance **1b**; f_a and f_b represent intensity factors of C(3′) and C(2′) of **1b**. It follows that the ^{13}C NMR singlet's intensity (I_S) is represented by

$$I_S{}^a = a(1 - b)f_a$$

$$I_S{}^{a'} = (I_s{}^a/\alpha) + [(\alpha - 1)/\alpha]\, I_N{}^a$$

where $I_N{}^a$ is the singlet intensity of C(3′) due to natural ^{13}C abundance **1b**, that the ^{13}C NMR doublet's intensity is represented by

$$I_D{}^a = abf_a$$

$$I_D{}^{a'} = abf_a/\alpha$$

and that

$$I_N{}^a = f_a c$$

By appropriate substitution and simplification,

$$I_S{}^{a'} = \frac{a(1 - b)f_a}{\alpha} = \left(\frac{\alpha - 1}{\alpha}\right) f_a c$$

$$= f_a\left[a' - a'b'\alpha + \left(\frac{\alpha - 1}{\alpha}\right) c\right]$$

but since $I_D{}^{a'} = (\alpha a')(\alpha b')f_a/\alpha = a'b'\alpha f_a$,

$$I_S{}^{a'} = f_a a' - I_D{}^{a'} + [(\alpha - 1)/\alpha]f_a c$$

from which division by $I_N{}^a$ gives

$$\frac{I_S{}^{a'}}{I_N{}^a} = \frac{a'}{c} - \frac{I_D{}^{a'}}{I_N{}^a} + \frac{\alpha - 1}{\alpha}$$

which rearranges to

$$\frac{a'}{c} = \left(\frac{I_S{}^{a'}}{I_N{}^a} + \frac{I_D{}^{a'}}{I_N{}^a} - 1\right) + \frac{1}{\alpha} \tag{3}$$

Similarly, it can be derived that

$$\frac{b'}{c} = \left(\frac{I_S{}^{b'}}{I_N{}^b} + \frac{I_D{}^{b'}}{I_N{}^b} - 1\right) + \frac{1}{\alpha} \tag{4}$$

Since

$$\frac{I_D{}^{a'}}{I_N{}^a} = \frac{a'b'\alpha f_a}{f_a c} = \frac{a'b'\alpha}{c}$$

it follows that

$$a'b' = \frac{c}{\alpha}\left(\frac{I_D{}^{a'}}{I_N{}^a}\right) \tag{5}$$

or, similarly,

$$a'b' = \frac{c}{\alpha}\left(\frac{I_D{}^{b'}}{I_N{}^b}\right) \tag{6}$$

Let

$$F_a = \left(\frac{I_S{}^{a'}}{I_N{}^a} + \frac{I_D{}^{a'}}{I_N{}^a} - 1\right)$$

and

$$F_b = \left(\frac{I_S{}^{b'}}{I_N{}^b} + \frac{I_D{}^{b'}}{I_N{}^b} - 1\right)$$

Equations 3 and 4 now can be rewritten as

$$a' = cF_a + c/\alpha \tag{7}$$

and

$$b' = cF_b + c/\alpha \tag{8}$$

From substitution of eq 7 and 8 into eq 5 and 6

$$c^2\left(F_a + \frac{1}{\alpha}\right)\left(F_b + \frac{1}{\alpha}\right) = \frac{c}{\alpha}\left(\frac{I_D{}^{a'}}{I_N{}^a}\right) = \frac{c}{\alpha}\left(\frac{I_D{}^b}{I_N{}^b}\right)$$

which rearranges to give

$$c\left(\frac{1}{\alpha}\right)^2 + \left[c(F_a + F_b) - \left(\frac{I_D{}^a}{I_N{}^a}\right)\right]\frac{1}{\alpha} + cF_aF_b = 0$$

then solving for $1/\alpha$ gives

$$\frac{1}{\alpha} = \left\{\frac{I_D{}^{a'}}{I_N{}^a} - c(F_a + F_b) \pm \sqrt{\left[c(F_a + F_b) - \frac{I_D{}^{a'}}{I_N{}^a}\right]^2 - 4c^2F_aF_b}\right\} \Big/ 2c \tag{9}$$

From the appropriate ^{13}C NMR area weights the following values can be calculated:

$$I_D{}^{a'}/I_N{}^a = 6.20$$

$$I_D{}^{b'}/I_N{}^b = 5.57$$

$$F_a = 6.83$$

$$F_b = 6.00$$

If the average of these $I_D{}^{a'}/I_N{}^a$ and $I_D{}^{b'}/I_N{}^b$ values (5.88) is used to solve eq 9, $\alpha = 12.72$, from eq 7, $a' = 0.0725$, and from eq 8, $b' = 0.0704$. Since $a = \alpha a'$ and $b = \alpha b'$ by definition, $a = 0.922$ and $b = 0.896$.

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Registry No.—**1a**, 5746-86-1; **1a** 2HCl, 67209-89-6; [2′,3′-$^{13}C_2$]-**1a**, 67209-83-0; **1b** 2HCl, 67209-84-1; [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b**, 67209-85-2; [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b**, 67209-86-3; 1b monoethanesulfonate salt, 67209-87-4; [2′,3′,*N*-CH_3-$^{13}C_3$]-**1b** monoethanesulfonate salt, 67209-88-5; **3**, 532-12-7; **4**, 67209-90-9; **5**, 67209-91-0; **6**, 67209-92-1; **7**, 67209-93-2; **10**, 67209-94-3; **11A** 67209-95-4; **11S**, 67209-96-5; **12A**, 67209-97-6; [1′,2′-$^{13}C_2$]-**12A**, 67209-98-7; [1′,2′-$^{13}C_2$]-**13**, 67209-99-8;

13, 67210-00-8; **14**, 3000-81-5; **16**, 930-41-6; **17**, 67210-01-9; **18**, 67210-02-0; **19**, 67210-03-2; 2,2-bis(ethylthio)ethanal, 42919-45-9; 1,1-bis(ethylthio)methane, 4396-19-4; 2-formyl-1,3-dithiane, 34906-12-2; 1,3-dithiane, 505-23-7; 1-acetyl-2,2-bis(ethylthio)ethanol, 67210-04-2; 2,2-bis(ethylthio)ethanol, 67210-05-3; 2-acetoxymethyl-1,3-dithiane, 67210-06-4; 1,3-dithiane-2-methanol, 37721-88-3; 1-acetyl-2,2-bis(ethylthio)ethanol sulfoxide, 67210-07-5; 3-acetylpyridine, 350-03-8; methoxyamine hydrochloride, 593-56-6; [1′,2′-$^{13}C_2$]-3-acetylpyridine, 67210-08-6; 3-bromopyridine, 626-55-1; 3-lithiopyridine, 60573-68-4; 3-ethylpyridine hydrochloride, 67210-09-7; 3-acetylpyridine hydrochloride, 67210-10-0; [1′,2′-$^{13}C_2$]-3-acetylpyridine methoxine, 67210-11-1; carbon-13 dioxide, 1111-72-4.

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Characterization of the Products of Alkylation of 2′-Deoxyadenosine and 2′-Deoxyguanosine by Chloroethyl Ethyl Sulfide

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Alkylation of 2′-deoxyadenosine by 2-chloroethyl ethyl sulfide (CEES) in aqueous solutions at pH 6.0 and 25 °C led to two products. These have been isolated and characterized on the basis of mass spectrometry, nuclear magnetic resonance spectroscopy, and ultraviolet spectroscopy as 2′-deoxy-1-[2-(ethylthio)ethyl]adenosine and 2′-deoxy-N^6-[2-(ethylthio)ethyl]adenosine. The products formed from 2′-deoxyguanosine under these same conditions were identified as 2′-deoxy-7-[2-(ethylthio)ethyl]guanosine and 2′-deoxy-N^2-[2-(ethylthio)ethyl]guanosine, and the corresponding pair of deribosylated alkylated purines.

The mutagenic activity of mustard gas first implicated DNA as an important site of biological alkylation in 1946.[1] Subsequently, other alkylating agents also have been studied in an attempt to relate the chemical nature of DNA alkylation to the observed biological changes.[2,3] While cross-linking of DNA strands has been implicated as an important reaction for bifunctional agents such as mustard gas [bis(2-chloroethyl) sulfide],[4] different mechanisms have been proposed for compounds capable of only single site attack.

2-Chloroethyl ethyl sulfide is a monofunctional alkylating agent capable of both mutagenic and lethal effects in *E. coli*.[5] These different physiologic effects may reflect different molecular changes in the DNA and thus precise definition of the latter is important. Studies on other sulfur mustards have shown predominant alkylation of guanine and adenine bases in nucleic acids[16] and thus these bases have been emphasized in the present studies.

Another reason for study of CEES reactions is that it is a relatively large molecule which might be expected to participate in chemical reactions differing from those of the simpler, well-studied, methylating mutagens.[3,6-8] Identification of CEES adducts in DNA may provide a useful extension of earlier biological studies[5] as well as models for the alkylation reactions of bifunctional mustard gas. Some of the adducts formed may be short lived in vitro and this may be related to temporal changes in vivo.

Although acid hydrolysis of DNA and RNA has been employed in many of the earlier studies of alkylation of nucleic acids, it is now understood that some alkylation products will be destroyed by such conditions. Thus nucleoside adducts were chosen for characterization as reference compounds, since they can be released from polymers by enzymatic procedures instead of chemical hydrolysis (i.e., nucleoside monophosphates produced by deoxyribonuclease and nucleosides obtainable by subsequent digestion with alkaline phosphatase). Historically, nonaqueous solvents often have been used in alkylation studies of this kind to enhance yields, and pH values are sometimes varied. However, the more physiologically relevant aqueous medium was used in this study and the pH was held near the physiologic value. The structural studies reported here rely on spectroscopic techniques consistent with the limited amount of sample available.

Materials and Methods

2′-Deoxyadenosine (dA) and 2′-deoxyguanosine (dG) were obtained from Sigma Chemical Co. 2-Chloroethyl ethyl sulfide (CEES) was obtained from Chemical Procurement Laboratories. Sephadex G-10 was obtained from Pharmacia Fine Chemicals.

Nucleoside Alkylation. Solutions of deoxyadenosine (10 mg/mL) or deoxyguanosine (4 mg/mL) were prepared in deionized water at room temperature. Fifteen milliliters of the nucleoside solution and 40 μL of 2-chloroethyl ethyl sulfide were mixed at room temperature. The pH of the mixture was maintained at 6.0 while the reaction was shaken for about 1 hr. Little or no subsequent alkylation could be observed.

The reaction mixture was then applied to an 80 × 2.8 cm column of Sephadex G-10 and eluted with 50 mM ammonium formate, pH 6.5 at 27 °C. Twenty milliliter fractions were collected at a flow rate of 80 mL/h. Ultraviolet absorption of the column effluent was continuously measured with an LKB UV recorder set at a wavelength of 254 nm. Collection tubes were pooled for each component in the effluent and subjected to prolonged lyophilization. This resulted in sublimation of both water and ammonium formate from the sample, leaving the purified reaction products.

Ultraviolet Spectroscopy. Ultraviolet spectra were recorded using a Cary Model 14 recording spectrophotometer and a 1 cm light path. Spectra were measured at pH 7, 1, and 11.

Mass Spectrometry. Electron impact mass spectra of trimethylsilylated samples[9,10] were recorded on a DuPont 21-110 instrument with ion source temperature 200 °C and ionizing voltage 70 eV. The chemical ionization mass spectra were obtained on a DuPont 491 instrument, using isobutane reagent gas at 200 °C.

Field desorption mass spectra were measured on a Varian CH 5 DF instrument operating under control of an Incos Model 2000 data system at nominal resolution of 1500. The magnet was scanned quadratically from *m/e* 900 to *m/e* 10 in 20 s.

Nuclear Magnetic Resonance. Ambient ^{1}H NMR spectra were recorded on Varian HA-100, JEOL-FX-100, and Varian HR-220 MHz NMR spectrometers equipped with fast Fourier transform units. Traces of *tert*-butyl alcohol and tetramethylsilane were added to the D_2O and Me_2SO-d_6 solutions, respectively, as internal standards. Up to 10 000 pulses were accumulated for each sample, using 8000 point data files. The guanine adduct, dGV, was dissolved in D_2O at pH 1.4. Otherwise, solutions were neutral. Deoxyguanine adducts were difficult to solubilize, hence NMR signals were not consistently strong.

Characterization of the Adducts

Alkylation of 2′-Deoxyadenosine. The profile of ultraviolet chromophores eluted from the Sephadex G-10 column is shown in Figure 1. Three compounds were detected, which are labeled dAI, dAII, and dAIII. On standing, product dAI

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Table I. The Chemical Shift Values of ^1H NMR Resonances of Deoxyadenosine and Deoxyguanosine Products in D_2O and Me_2SO-d_6

	dAI		dAIII		dGI		dGV	
	Me_2SO-d_6	D_2O	Me_2SO-d_6	D_2O	Me_2SO-d_6	D_2O	Me_2SO-d_6	D_2O
CH_3CH_2	1.15[a] (t,[b] J = 7.2[c])	1.18 (t, J = 7.2)	1.10 (t, J = 7.2)	1.15 (t, J = 7.2)	1.15 (t, J = 7.5)	1.21 (t, J = 7.3)	1.15 (t, J = 7.2)	1.16 (t, J = 7.2)
CH_3CH_2	2.53 (q, J = 7.2)	2.57 (q, J = 7.2)	~2.50	2.54 (q, J = 7.2)	d	2.51 (q, J = 7.1)	d	2.50 (q, J = 7.2)
$-SCH_2CH_2-$	2.85 (t, J = 6.5)	3.08 (t, J = 6.2)	3.05 (t, J = 6.5)	3.14 (t, J = 6.5)	2.99 (t, J = 6.5)	3.09 (t, J = 6.1)	2.92 (t, J = 6.5)	3.02 (t, J = 6.5)
$-CH_2CH_2N-$	4.14 (t, J = 6.5)	4.54 (t, J = 6.4)	4.44 (t, J = 6.4)	4.70 (t, J = 6.5)	4.29 (t, J = 6.5)	d	4.03 (t, J = 6.5)	4.53 (t, J = 6.5)
H-C-1′	6.18 (pt, J = 6.6, 6.6)	6.52 (pt, J = 6.6, 6.6)	~6.46	d	d	6.42 (t, J = 5.6)		
H_2-C-2′	~2.30 (m)	~2.76 (m)	d	d	d	d		
H-C-3′	4.33 (m)	4.7 (m)	d	d	d	d		
H-C-4′	3.81 (m)	~4.18 (m)	d	d	d	d		
H_2-C-5′	3.50 (m)	3.80 (m)	d	d	d	d		
H-C-2 (dA) or H_2-N-2 (dG)	8.06 (s)	8.48 (s)	~7.9 (s)	d	6.19 (s)		6.06 (s)	
H-C-8	8.12 (s)	8.52 (s)	~8.34 (s)	d	7.88 (s)		7.85 (s)	8.62 (s)

[a] All chemical shifts values are in ppm from Me_3Si in Me_2SO-d_6 or from DSS in D_2O. [b] Abbreviation used as: t = triplet, q = quartet, pt = pseudotriplet, m = multiplet, s = singlet. [c] Coupling constant, in Hz. [d] These resonances are either too broad or too weak, or shaded by other peaks due to impurities, limited sample solubility, or limited sample.

was observed to be converted slowly to dAIII.

All three compounds were converted to trimethylsilyl derivatives whose electron impact mass spectra were measured. The mass spectrum of trimethylsilylated dAII was identical to that of the trimethylsilyl derivative of the starting material, deoxyadenosine, with a molecular ion peak at *m/e* 467. The spectra of the derivatives of both dAI and dAIII contain molecular ion peaks at *m/e* 555, an increment of 88 mass units relative to the derivatized starting material. This molecular weight is consistent with the presence of three trimethylsilyl groups and one ethylthioethylene moiety on each nucleoside molecule. The presence of three sites for silylation on both of the product molecules provides evidence that alkylation has occurred on the base, rather than on the sugar moiety. This is further confirmed by electron impact induced cleavage of bis(trimethylsilyl)deoxyribose, leading to a B + H peak[9] at *m/e* 295. Alkylation at N-7 leading to a quaternary ammonium center is also ruled out, since presence of the latter structure is known to cause oxidation at position 8 during the derivation reaction.[11] The masses of molecular ions and fragment ions observed exclude 8-oxo or ring-opened analogues. Both M-15 and M-88 peaks are present (*m/e* 540 and 467), corresponding to loss of CH_3 and C_4H_8S from the molecular ion. The base peak in each spectrum occurs at *m/e* 207 and represents ions formed by the loss of both the bis(trimethylsilyl)deoxyribose moiety (accompanied by transfer of a hydrogen atom) and the ethylthioethylene moiety (accompanied by hydrogen transfer). A number of other peaks in the spectrum, e.g., *m/e* 217, are characteristic of trimethylsilylated deoxyribose.[9]

Although generally similar, the two spectra are distinguishable by two interesting peaks at *m/e* 480 and 220, which are both prominent in the spectrum of dAIII. These fragment ions arise by cleavage of $C_2H_5SCH_2$ from the alkyl side chain, the former from the molecular ion and the latter accompanying the loss of silylated deoxyribose with hydrogen transfer. This α cleavage is associated with the structure alkylated at N^6 (*vide infra*) and presumably reflects the influence of the charged exocyclic (aliphatic) nitrogen as compared to the highly conjugated N-1 site.

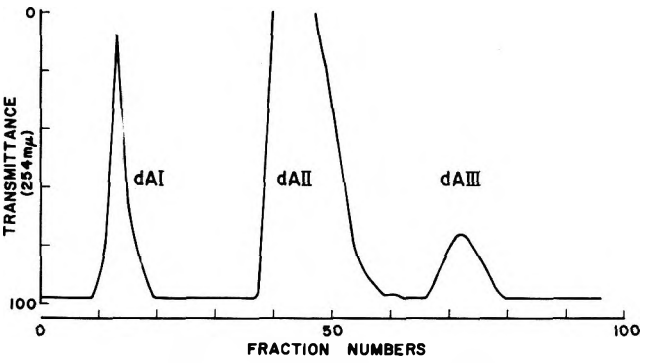


Figure 1. Chromophoric profile of the product mixture from the alkylation of deoxyadenosine.

The molecular weight of dAI was confirmed by observation of an M + 1 base peak at *m/e* 556 in the chemical ionization mass spectrum of the trimethylsilyl derivative and of an M + 1 base peak at *m/e* 340 in the field desorption spectrum of the underivatized adduct.

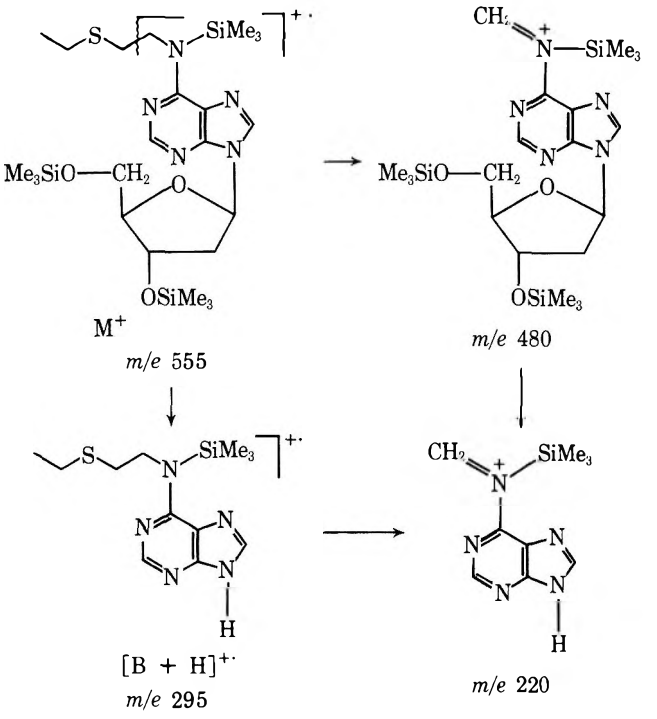
The chemical shift values (in ppm) of the proton resonances of compounds dAI and dAIII in D_2O and Me_2SO-d_6 are listed in Table I. The NMR spectra of both adducts contain four more signals than the spectrum of the starting material, 2′-deoxyadenosine. These occur as triplets at 1.15, 2.85, and 4.14 ppm and a quartet centered at 2.53 ppm (half of which is buried in the Me_2SO-d_6 peak from the solvent). Two triplets and the quartet integrate to about two protons, while the third triplet represents three protons. The position and size of these signals suggests that both dAI and dAIII contain one $-CH_2CH_2-$ group and one CH_2CH_3 group and that one ethylthioethylene moiety has been added to each nucleoside by the alkylation reaction. No direct evidence could be obtained for the sites of alkylation. However, alkylation at N-7 or C-8 is excluded by the persistence of H-8 resonance in D_2O.[12]

The site of alkylation on the purine base was assigned primarily by ultraviolet spectroscopy. Table II shows the ultraviolet spectra of the three compounds isolated from the re-

Table II. Maximum Absorption (nm) in Ultraviolet Spectra of Products[a]

compd	registry no.	pH 7	pH 1	pH 11
2′-deoxy-1-[2-(ethylthio)ethyl]adenosine (dAI)	66792-45-8	260	260	260 (268)
2′-deoxyadenosine (dAII)	958-09-8	259	257	259
2′-deoxy-N^6-[2-(ethylthio)ethyl]adenosine (dAIII)	66792-46-9	262	263	268
2′-deoxy-7-[2-(ethylthio)ethyl]guanosine (dGI)	66901-78-8	250, 284	253 (280)	267
2′-deoxyguanosine (dGII)	961-07-9	255 (270)	255	258–268
2′-deoxy-N^2-[2-(ethylthio)ethyl]guanosine (dGIII)	66792-47-0	253.5 (280)	257 (285)	258 (274)
N^2-[2-(ethylthio)ethyl]guanine (dGIV)	66792-48-1	247, 278	251, 280	274
7-[2-(ethylthio)ethyl]guanine (dGV)	693-07-2	283, 245	250, 276	280, 240

[a] Values for reference compounds[8,13,14,19,29–31] removed at referee's request.



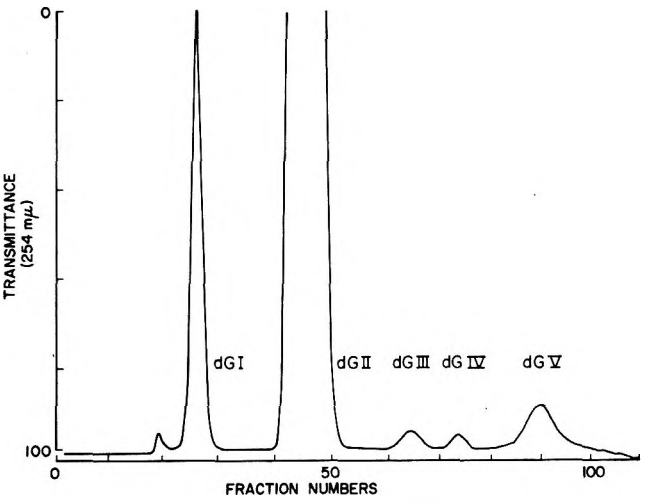


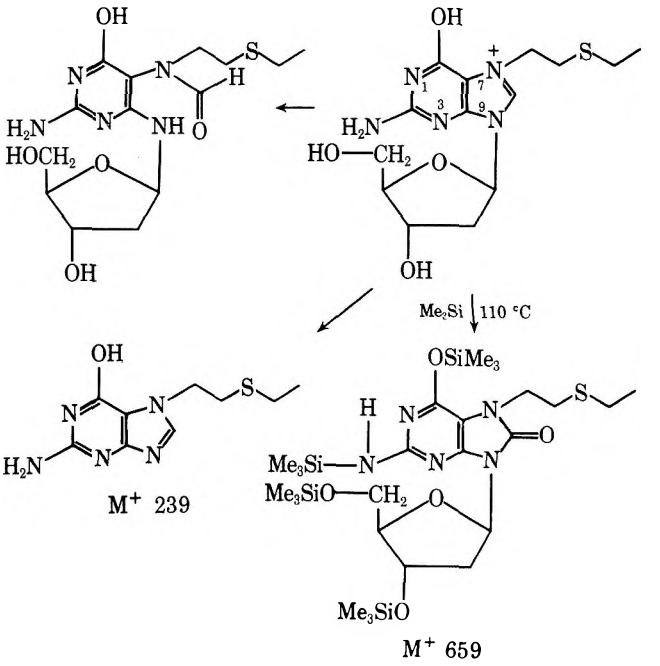
Figure 2. Chromophoric profile of the product mixture from the alkylation of deoxyguanosine.

action of deoxyadenosine with chloroethyl ethyl sulfide and references to published values for isomeric monomethylated and monoethylated deoxyadenosine and adenosine. pK_A values and corresponding ultraviolet absorption spectra for alkylated purine nucleosides provide no information about the nature of nonchromophoric substituents but rather reflect primarily the site of alkylation on the purine.[14,19,20] On the basis of the values in Table II, product dAI was assigned as 2′-deoxy-1-[2-(ethylthio)ethyl]adenosine and product dAIII was assigned as 2′-deoxy-N^6-[2-(ethylthio)ethyl]adenosine. Compound dAII is unreacted deoxyadenosine. The observed spontaneous conversion of dAI to dAIII further supports these assignments, since isomerization of N-1 alkylated adenosine to N^6-alkylated adenosine is well documented.[15]

Alkylation of 2′-Deoxyguanosine. The profile of ultraviolet chromophores eluted from the Sephadex G-10 column is shown in Figure 2. The five compounds labeled dGI through V were collected and characterized. The material in peak dGI was spontaneously converted to that in peak dGV on standing for several days.

Peak dGII was found to be unreacted starting material, deoxyguanosine, based on its UV spectra (Table II), the mass spectrum of its tetrakis(trimethylsilyl) derivative (M^+ 555), and the elution from the column coincident with authentic material.

Peak dGI was characterized by UV and NMR spectroscopy and by several kinds of mass spectrometry. The UV spectra obtained at pH 1, 7, and 11 (Table II) suggest that the dGI adduct is a 7-alkylated deoxyguanosine. Field desorption spectra measured on an underivatized dGI sample did not contain peaks corresponding to nucleoside molecular ions, rather a mono(ethylthioethyl)guanine was identified, with a base peak at *m/e* 239. An electron impact mass spectrum of the trimethylsilyl derivative of dGI contained a molecular ion peak at *m/e* 659, accompanied by an M − 15 peak at *m/e* 644. This is consistent with the structure shown in the scheme, in which the alkylated nucleoside carries four trimethylsilyl groups and an 8-oxo group. Such oxidation is well documented at C-8 in trimethylsilylation of 7-alkylated guanosine[10,11] and confirms N-7 as the site of alkylation. In addition to the ex-



pected B + H peak at *m/e* 399, intense peaks at *m/e* 383 and 368 confirm the presence of (ethylthioethyl)guanine in the sample before silylation, presumably formed by deribosylation after chromatography.

Nuclear magnetic resonance spectra of dGI also supported the identification of this adduct as 2′-deoxy-7-[2-(ethylthio)-ethyl]guanosine. Resonances in both D_2O and Me_2SO-d_6 are shown in Table I. One methyl and three methylene groups in the ethylthioethylene side chain are discernable as in the two deoxyadenosine adducts discussed above. In Me_2SO-d_6 protons on N^2 and C-8 were detected eliminating these as positions of substitution. The 1′-carbohydrate proton was characterized in the spectrum run in D_2O. The extended times (up to 12 h) employed in the Fourier transform technique, necessitated by limited sample solubility, had the disadvantage of permitting substantial deribosylation to take place during the measurements. As these proceeded, the initially clear D_2O solution became cloudy and a new set of signals appeared, which were similar to those from dGV. This facile deribosylation is considered characteristic of 7-alkylated guanosines.[14,19]

Alkylation at N-7 in guanosines is also known to promote opening of the imidazole ring with the addition of the elements of water, as shown in the scheme above.[14,19,21] This reaction is usually promoted by alkali. Indeed, when the product mixture from the alkylation of deoxyguanosine by CEES was adjusted to pH 7 before application to the Sephadex column, dGI was isolated in which the imidazole ring was opened. The ring-opened and ring-closed N-7 adducts had similar retention factors on the column, both eluting ahead of unreacted 2′-deoxyguanosine.

Ultraviolet spectroscopic measurements on the base-treated dGI adduct confirmed its ring-opened structure (Table II). The mass spectrum of a trimethylsilyl derivative of this material was measured using electron impact ionization. The molecular weight of 661 daltons is consistent with a tetrakis-(trimethylsilyl) derivative of deoxyguanosine carrying one ethylthioethyl group, in which the five-membered imidazole ring has been opened with the addition of the elements of water. Electron impact induced loss of the sugar moiety leads to B^+ ions and $B^+ - 15$ ions (*m/e* 400 and 385, respectively), confirming that the ethylthioethylene group is attached to the base. However, the alkyl group is cleaved as readily as the sugar, leading to M − 88 (*m/e* 573) and B + H (*m/e* 313) ions.

The chemical ionization mass spectrum of the trimethylsilyl derivative of the base-treated dGI sample was also measured. The protonated molecular ion peak at *m/e* 662 is the base peak in the spectrum and is consistent with the assignment of the sample as a tetrakis(trimethylsilyl)ethylthioethyldeoxyguanosine in which the imidazole ring has been opened with the addition of water. B + 2 H ions of mass 402 also contribute an intense peak to the spectrum.

The electron impact mass spectrum of trimethylsilylated material from peak dGIII contains molecular ions and M − 15 peaks at *m/e* 643 and 628, respectively, consistent with the tetrakis(trimethylsilyl) derivative of an adduct of deoxyguanosine carrying one 2-(ethylthio)ethyl group. Alkylation at positions 1 and O^6 is eliminated by the attachment of four trimethylsilyl groups. The trimethylsilylation conditions used in this study put only one trimethylsilyl group on the primary amine at the N^2 position in deoxyguanosine. However, under these same conditions, one trimethylsilyl group is also attached to a secondary amine such as 2′-deoxy-N^2-(methyl)-guanosine. Thus alkylation at N^2 is not eliminated as a possibility by formation of the tetrakis(trimethylsilyl) derivative.

Titration curves were particularly useful in the characterization of peak dGIII. Ionization was determined as a function of pH by calculating extinction ratios of UV absorption at 270/250 and 280/260 nm. A second pK_A inflection, around pH 9.5, indicates that the monoalkylated deoxyguanosine eluted at peak dGIII is substituted at position 8 or N^2 and not at 1 or O^6.[14,22]

The final assignment of dGIII as 2′-deoxy-N^2-[2-(ethylthio)ethyl]guanosine was based on the maxima and shapes[20] of complete ultraviolet spectra scanned at pH 1, 7, and 11. These maxima are reported in Table II and are clearly distinguishable from those characteristic of deoxyguanosine or guanosine alkylated at other positions, including C-8.

The electron impact mass spectrum of trimethylsilylated peak dGIV contained M^+ and $(M - 15)^+$ peaks at *m/e* 455 and 440, consistent with the structure of a tris(trimethylsilyl) derivative of a deribosylated mono(ethylthioethyl)guanine. Characteristics of UV spectra of dGIV obtained at several pH values are presented in Table II. The maxima and overall shape of the absorption curves[20] match those of N^2-alkylguanines and are distinctive from guanines alkylated at other positions. Thus dGIV is identified as N^2-[2-(ethylthio)-ethyl]guanine by its UV spectra and by its relationship to dGIII.

The electron impact mass spectrum of trimethylsilylated dGV contains M^+ and $(M - 15)^+$ ions at *m/e* 383 and 368, suggesting that the sample is a bis(trimethylsilyl)monoalkylguanine derivative.

Table I shows chemical shift values from the ^1H NMR spectrum of dGV. Protons are detected for equimolar amounts of ethylthioethylene and guanine, but ribosyl protons are absent. The sample had very limited solubility in water at pH 7, and the measurements in Table I were made at pH 1.4. The C^8–H chemical shift is very close to that of C^8–H in guanine measured under similar conditions (8.53 ppm). One methylene group in the side chain is moved downfield about 0.23 ppm, confirming the assignment of the purine-bonded methylene signal. Other proton signals are unaffected by the pH change.

The UV characteristics of dGV are listed in Table II. The maxima and also the shapes[20] of the UV curves are identical with those of authentic 7-alkylguanines and distinct from guanines alkylated at other positions. Thus, dGV is identified as 7-[2-(ethylthio)ethyl]guanine.

Discussion

Deoxyadenosine and adenosine have been shown to be methylated by a variety of agents primarily at N-1.[3,6,7,14] Although positions N-3 and N-7 are also considered active, only the latter has been found to be substituted as a product of nucleoside methylation and that only rarely.[6,14,18] Although direct methylation is considered not to occur at exocyclic N^6,[7] mutagens that transfer alkyl groups larger than methyl have been observed to alkylate the N^6 position of adenosine.[7,8] Thus, the products formed by the reaction of CEES and deoxyadenosine are consistent with the general chemistry of adenosine nucleosides.

The alkylation reactions of two compounds closely related to CEES, bis(2-chloroethyl) sulfide and 2-hydroxyethyl 2-chloroethyl sulfide, have been studied by Shooter et al.[16] and Lawley et al.[17] Polyadenylic acid, bacteriophage DNA, and bacteriophage RNA were the substrates. Alkylated polymers were hydrolyzed by combinations of enzymatic and chemical steps, and the resulting modified adenines and adenylic acids were characterized by their chromatographic mobility and ultraviolet spectra. Adenine and adenylate adducts were reported to be alkylated at N-1, N-3, and N^6. A major difference between the results of Shooter and Lawley and those reported here is the recovery by the earlier workers of 3-alkylated adenine from polymers. This difference between the reactivity of polymers and adenine nucleosides appears to be general.[14,18]

Since authentic standards were not available for co-chromatography with some of the polymer-derived products in the earlier studies, the present characterization of deoxyadenosines alkylated at N-1 and N^6 by closely related CEES strengthens previously reported structure assignments.

Deoxyguanosine and guanosine are alkylated most readily at position 7; however, adducts of these nucleosides carrying alkyl groups at 1, N^2, and O^6 [14,23,29] also have been characterized. Guanine adducts alkylated at 3, 7, O^6 and N^2 have been isolated from polyguanylic acid, DNA, and RNA.[10,14,23-28] In particular, bis(2-chloroethyl) sulfide and 2-chloroethyl 2-hydroxyethyl sulfide have been shown to alkylate guanine at N-7 in DNA and RNA in vivo and in vitro.[4,16,17] No guanine positions other than N-7 have been reported to be alkylated by these two sulfur mustards. Thus, the alkylation at N-7 of deoxyguanosine by CEES was anticipated. Alkylation by CEES at N^2 is of greater interest because all the N^2-mono adducts found heretofore in nucleosides and polymers (i.e., excluding guanine itself) have been formed from epoxides of massive polycyclic hydrocarbons.[23-26] The present work demonstrates that a medium sized substituent also can be attached to N^2, and, presumably, by an alkylation mechanism different from that of the epoxides.[3,32] It seems likely that N^2-alkylation of nucleosides and nucleic acids is more general than previously recognized. The 2′-deoxy-7-[2-(ethylthio)ethyl]guanosine and N^2-[2-(ethylthio)ethyl]-guanine adducts reported here are unstable in acid and would have been destroyed by the acid hydrolysis of polymers used by some previous investigators.

The products characterized here can be used as standards for characterization of nucleoside ^{35}S adducts from CEES-alkylated deoxyribonucleic acid.

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Registry No.—CEES, 693-07-2.

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Studies Directed toward a Total Synthesis of Nucleoside Q. The Annulation of 2,6-Diaminopyrimidin-4-one with α-Halo Carbonyls to Form Pyrrolo[2,3-*d*]pyrimidines and Furo[2,3-*d*]pyrimidines

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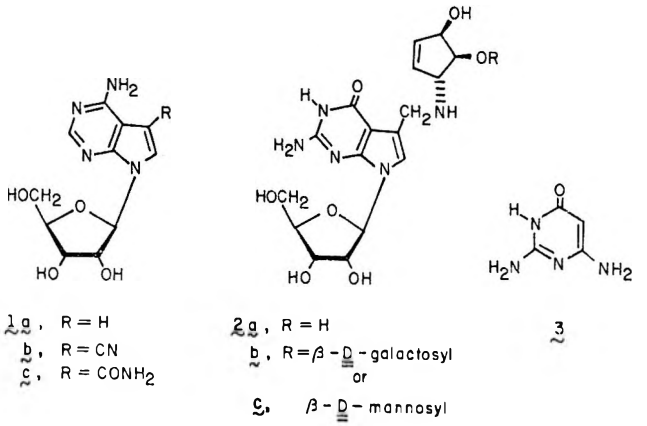
The condensation of 2,6-diaminopyrimidin-4-one (**3**) with various α-halo carbonyl compounds is examined. The reaction produces two types of products, both regiospecifically. For example, treatment of **3** with α-chloroacetone affords 2-amino-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (**5a**) and 2,4-diamino-5-methylfuro[2,3-*d*]pyrimidine (**6a**). Depending upon the nature of the α-halo carbonyl compound, pyrrolo[2,3-*d*]pyrimidin-4-one and/or furo[2,3-*d*]pyrimidine products were observed. Structural assignments were based on UV, ^{1}H NMR, and ^{13}C NMR. 2-Chloropropionaldehyde was found to react with **3** to produce 2-amino-5-methylpyrrolo[2,3-*d*]pyrimidin-4-one (**7**) exclusively, thus providing an entry into the substitution pattern of nucleoside Q (**2**).

The pyrrolo[2,3-*d*]pyrimidine ring system has aroused considerable interest due to its presence in several natural products. It is contained in the nucleoside antibiotics tubercidin (**1a**), toyocamycin (**1b**), and sangivamycin (**1c**),[2] as well as in the more recently characterized hypermodified nucleosides Q (**2a**)[3] and Q* (**2b** and **2c**).[4] Both Q and Q* are present in the initial position of the anticodon in tyrosine, aspartate, asparagine, and histidine tRNA from various organisms.[5]



1 a, R = H; b, R = CN; c, R = $CONH_2$

2 a, R = H; b, R = β-D-galactosyl or c, β-D-mannosyl

3

Since Q in that position may not have a major effect on protein synthesis, a regulatory function has been suggested, though no definitive evidence is yet available. Interest in Q and its biological properties, coupled with its unique structure (it is the only skeletally modified nucleoside thus far isolated from RNA) and lack of availability in quantity, have prompted several groups to direct efforts toward its synthesis,[6-11] with one success reported thus far.[12] General entry into the pyrrolo[2,3-*d*]pyrimidine system has been achieved (a) from pyrrole-based precursors by formation of the pyrimidine ring,[13-15] (b) from pyrimidines with a 5-acetaldehyde or acetone side chain and adjacent amino group by cyclization with acid,[16-18] (c) from 4-pyrimidinylhydrazones by a thermally induced reaction analogous to the Fischer indole synthesis,[19,20] and (d) by condensation of 2-amino-6-alkylamino-4-hydroxypyrimidines, 6-aminouracil, and several other related compounds with aqueous chloroacetaldehyde.[16,21] The only approaches that have been utilized specifically for the 7-deazaguanine system contained in nucleoside Q are (b)[6,9,12] and the modification of the intact pyrrolo[2,3-*d*]pyrimidine ring in tubercidin and toyocamycin.[7,8]

Our strategy, based on the chloroacetaldehyde precedent, was to build the pyrrole ring onto a preformed pyrimidine ring, thus generating the 7-deazaguanine ring directly. By employing the appropriate α-halo carbonyl compound, substituents might be introduced into the pyrrole ring, later to be elaborated to the side chain of Q. Specifically, we present the initial results of our investigation of the reactions of various α-halo carbonyls with 2,6-diamino-4-pyrimidinone (**3**). We have determined the sites of attack, the major products, and the regiochemistry of the reaction.

Results and Discussion

In principle, an α-halo carbonyl compound might annulate **3** in a variety of ways. In addition to the aforementioned precedent for pyrrolo[2,3-*d*]pyrimidine formation, chloroacetaldehyde is well known to condense at two nitrogens to form a fused imidazo ring, as seen in its reactions with cytosine and adenine-containing moieties.[22] No precedent for the formation of a furo[2,3-*d*]pyrimidine by this route exists to our knowledge, though thieno[2,3-*d*]pyrimidines are formed with a 4-thio substituent present.[23]

Chloroacetone was chosen as the initial substrate, and proved to be representative of all the α-halo ketones that we examined. Stirring an excess of α-chloroacetone with **3** in DMF at 55 °C for 2 days afforded two products, **5a** (55%) and **6a** (20%), which were readily separated chromatographically. Other solvents gave the same two products, but DMF in general resulted in superior yields under more moderate conditions. That both products were the result of condensation at C-5 of the pyrimidine is easily determined from the ^{1}H NMR spectra, in which both **5a** and **6a** had only one vinyl proton; annulation by any other mode would produce two vinyl protons. A comparison of the ultraviolet spectra of **5a** and **6a** is presented in Figure 1. Though they are similar, the additional peak at 300 nm in the spectrum of **6a** in acid indicates that the two compounds have different chromophores. **5a** has UV, ^{1}H NMR, and ^{13}C NMR characteristics which readily allow assignment of the pyrrolo[2,3-*d*]pyrimidine system to it. However, depending upon the regiospecificity of the reaction, either the 5-methyl or the 6-methyl compound might be produced. Resolution of this question was possible via ^{13}C NMR data (Table II). The signal for C-6 (δ 126.1) remained a singlet during off-resonance decoupling, while C-5 (δ 98.5) split into a doublet, thus placing the methyl group at C-6. Also, **5a** has been prepared elsewhere by a different route,[6] and spectral data, including ^{13}C NMR resonances, are virtually identical. That the minor product is not the isomeric pyrrolo[2,3-*d*]pyrimidine is conclusively demonstrated by the UV spectrum, the presence of two groups of exchangeable protons (2 H each) at δ 6.2 and 6.4 in the ^{1}H NMR spectrum, and the dramatic differences in the ^{13}C NMR, to be discussed shortly. Also, in the ^{1}H NMR spectrum, the vinyl proton of **6a** occurs at δ 7.17, while for **5a** its chemical shift is δ 5.86. Thus, **6a** must be a furo[2,3-*d*]pyrimidine, since only one other direction of cyclization is possible. The question of the position

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Table I. Products from α-Halo Ketone Condensations with 3

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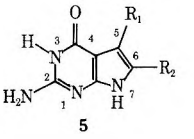

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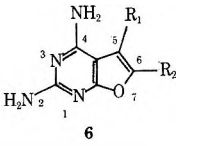

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a	R_1 = H; R_2 = CH_3; X = Cl	R_1 = H; R_2 = CH_3	R_1 = CH_3; R_2 = H
b	R_1 = H; R_2 = $CH_2CO_2CH_2CH_3$; X = Br	R_1 = H; R_2 = $CH_2CO_2CH_2CH_3$	
c	R_1 = R_2 = CH_3; X = Br	R_1 = R_2 = CH_3	R_1 = R_2 = CH_3
d	R_1 = CH_3; R_2 = C_6H_5; X = Br	R_1 = CH_3; R_2 = C_6H_5	
e	R_1 = C_6H_5; R_2 = CH_3; X = Br	R_1 = C_6H_5; R_2 = CH_3	
f	R_1 = $CH_2C_6H_5$; R_2 = CH_3; X = Br	R_1 = $CH_2C_6H_5$; R_2 = CH_3	
g	R_1 = H; R_2 = CH_2Cl; X = Cl		R_1 = CH_2Cl; R_2 = H
h	R_1, R_2 = $-(CH_2)_4-$; X = Cl		R_1, R_2 = $-(CH_2)_4-$

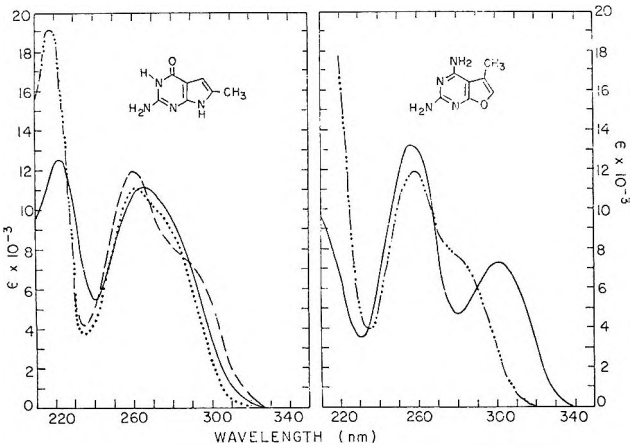


Figure 1. Ultraviolet absorption spectra of **5a** and **6a**: acid, —; pH 7, - - -; base, • • •.

of the methyl group is again readily resolved via the ^{13}C NMR spectrum (Table III), where C-5 (δ 93.0) remains as a singlet upon off-resonance decoupling, while C-6 (δ 133.4) splits into a doublet, thus placing the methyl at C-5 in **6a**.

Compound **5a** was initially isolated as the hydrochloride salt, and comparison of the ^{13}C NMR spectra of the neutral and protonated species (Table II) allows some conclusions to be drawn about the site of protonation. It has been observed that protonation (or alkylation) of a ring nitrogen will cause an upfield shift in the resonances of the adjacent carbons.[24-26] The large upfield shift of C-7a (13.6 ppm), together with the smaller upfield shifts of C-2 (1.5 ppm) and C-4 (2.6 ppm), make it likely that the major site of protonation in **5a** is N-1, with perhaps N-3 protonating to a much lesser extent. Conversion of **5a**·HCl to the free base was readily accomplished by stirring with Amberlite IR-45 (OH^- form).

A comparison of the ^{13}C NMR spectra of **5a** and **6a** (Tables II and III), which are indicative of other compounds prepared in this study, shows that resonances for C-2, C-4a, C-6, and C-7a all are considerably shifted downfield in **6a**, relative to **5a**. The outstanding characteristic, however, is certainly the position of C-7a at δ 169.4 in **6a** vs. δ 151.2 in **5a**. This signal, together with the aforementioned UV and ^1H NMR differences, allow facile assignment of each ring system for the other condensation reactions that we have examined.

For the series of α-halo ketones (**4a–h**) that we have examined, the products in all cases are pyrrolo[2,3-*d*]pyrimidines (**5**) and/or furo[2,3-*d*]pyrimidines (**6**) with substitution at C-5 and C-6 consistent with the pattern set forth in the chloroacetone case. The α-halo ketones and products are listed in Table I. Interestingly, ethyl 4-bromo-3-oxobutanoate (**4b**), 2-bromo-1-phenyl-1-propanone (**4d**), 1-bromo-1-phenyl-2-propanone (**4e**), and 3-bromo-4-phenyl-2-butanone (**4f**) give exclusively pyrrolo[2,3-*d*]pyrimidines, while 1,3-dichloroacetone (**4g**) and 2-chlorocyclohexanone (**4h**) afford only furo[2,3-*d*]pyrimidines. Chloroacetone (**4a**) and 2-bromo-3-butanone (**4c**) provide a mixture of the two ring systems. In order to contrast directly the change on going from a bromo to a chloro, 1-chloro-1-phenyl-2-propanone was also examined and was found to give substantially the same result as bromo compound **4e**, but at a much slower rate. In the cases (**5d** and **5e**) where the products differed only by the interchange of the methyl and phenyl at C-5 and C-6, ^{13}C NMR was utilized for positive structure identification. A phenyl substituent is known generally to cause a larger downfield shift in the carbon to which it is attached than a methyl group. Employing the dimethyl derivative **5c** for comparison purposes, C-5 in **5e** is 6.8 ppm downfield from C-5 in **5c**, while C-5 in **5d** is only 2.6 ppm downfield from C-5 in **5c**. This observation supports the structure expected based on the typical mode of addition. The same observation (in the reverse sense) applies to C-6 of **5d**, and hence it must be the positional isomer, as expected.

As has been alluded to earlier, the annulation reactions occur in a regiospecific manner. In cases where pyrrolo[2,3-*d*]pyrimidines are formed, the carbonyl carbon of the halo ketone becomes bonded to the 6-NH_2 of **3**, and the carbon attached to halogen is linked to C-5 of **3**. Furo[2,3-*d*]pyrimidine products are formed by bonding of the carbonyl carbon of the halo ketone to C-5 of **3**, with the carbon attached to halogen residing next to the oxygen at C-4 of **3**.

A variety of mechanistic possibilities exist to account for the bifurcate reaction of **3** and several precedents are worth mentioning. In the study where thieno[2,3-*d*]pyrimidines were isolated in a similar reaction, it was possible to adjust the conditions such that an S-alkylated intermediate was isolated.[23] In cases where a 5-acetaldehyde or 5-acetonyl side chain on a pyrimidine ring is cyclized to a furo[2,3-*d*]pyrimidine (via adjacent hydroxyl) or to a pyrrolo[2,3-*d*[pyrimidine (via adjacent amino), acidic conditions have been utilized.[16-18,27] For several reactions where aminopyrimidines annulate from nitrogen to nitrogen to form a fused imidazole ring, the carbonyl of the α-halo carbonyl becomes bonded to the exocyclic amino and the halogen-containing carbon to a ring nitrogen.[28-31] In a recent study kinetic evidence is presented to indicate that initial reaction occurs between the 6-amino of adenosine 5′-monophosphate and the carbonyl carbon of *chloroacetal*dehyde, followed by cyclization and loss of water.[32] Condensations involving β-dicarbonyls and aminopyrimidines, however, have been suggested to involve initial acylation at C-5 of the pyrimidine followed by ring closure.[33] The mechanisms leading to **5** and **6** must involve at least three major steps (not necessarily in this order): (1) bond formation between a heteroatom (O or N) of **3** and a carbon of the α-halo ketone, (2) bond formation between C-5 of **3** and a carbon of the α-halo ketone, and (3) loss of water. Additional steps would most likely be just prototropic shifts. Since under the reaction conditions employed no intermediates were isolated or were visible by thin-layer chromatographic analysis, no direct evidence is available.

Table II. ^{13}C Data for Pyrrolo[2,3-*d*]pyrimidines[a,b]

compd	registry no.	C_2	C_4	C_{4a}	C_5	C_6	C_{7a}	other carbons
5a	62981-82-2	152.2	158.7	99.8	98.5(d)	126.1	151.2	12.9 (CH_3, q)
5a (lit.[6])		151.8	158.4	99.9	98.6(d)	126.2	151.1	12.6 (CH_3, q)
5a·HCl	67194-80-3	150.7	156.1	100.1	99.9(d)	128.6	137.6	12.6 (CH_3, q)
5b	67226-39-5	152.0	158.5	99.8	100.6(d)	123.0	151.2	14.0 (CH_3, q), 33.1 (CH_2C=O, t), 60.3 (CH_2O, t), 170.0 (C=O)
5c	67194-81-4	151.1	158.3	99.4	108.1	122.1	145.6	9.4, 10.0 (2 CH_3, q)
5d	67194-82-5	152.4	159.6	100.9	110.7	125.7	151.2	11.2 (CH_3, q), 123.8 (d), 126.5 (d), 128.4 (d), 132.7 (aromatic)
5e	67194-83-6	151.7	158.0	97.6	114.9	123.6	148.6	11.5 (CH_3, q), 125.1 (d), 127.2 (d), 129.8 (d), 134.5 (aromatic)
5f	67226-40-8	151.6	158.9	98.8	111.8	122.1	149.9	10.4 (CH_3, q), 29.7 (CH_2, t), 125.0 (d), 127.9 (d), 128.2 (d), 142.7 (aromatic)
7	65062-57-9	152.1	159.4	99.4	112.9	113.5(d)	150.9	11.3 (CH_3, q)

[a] All resonances in ppm downfield from internal Me_4Si in Me_2SO-d_6. Letters in parentheses refer to multiplicities in off-resonance decoupled spectra. In cases where no multiplicity is shown, the resonance remained a singlet. [b] It is possible that certain assignments may be reversed in cases where resonances occur in close proximity and the multiplicities are identical.

Table III. ^{13}C Data for Furo[2,3-*d*]pyrimidines[a,b]

compd	registry no.	C_2	C_4	C_{4a}	C_5	C_6	C_{7a}	other carbons
6a	67194-84-7	161.1	159.2	114.3	93.0	133.4(d)	169.4	9.7 (CH_3, q)
6c	67194-85-8	160.2	158.4	107.8	93.9	141.3	167.8	9.4 CH_3, q), 10.6 (CH_3, q)
6g	67194-86-9	157.7	155.5	117.3	90.7	137.9(d)	169.3	37.0 (CH_2Cl, t)
6h	67194-87-0	158.3	156.3	110.9	92.6	145.3	168.0	21.05 (t), 21.97 (t), 22.12 (t) (tetramethylene bridge)

[a] All resonances in ppm downfield from internal Me_4Si in Me_2SO-d_6. Letters in parentheses refer to multiplicities in off-resonance decoupled spectra. In cases where no multiplicity is shown, the resonance remained a singlet. [b] It is possible that certain assignments may be reversed in cases where resonances occur in close proximity and the multiplicities are identical.

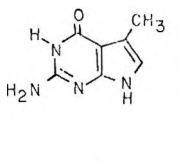
In an attempt to gain some insight into the general reaction, we have carried out some preliminary theoretical calculations on **3**.[34] The position of highest negative charge in the ground state is, in fact, N-6, while the atom with the highest electron density in the HOMO is C-5. In the electrophilic partner, the net positive charge and the coefficient of the LUMO of the carbonyl carbon of chloroacetone are considerably higher than the carbon attached to halogen. These calculations are consistent with the experimental data that we have gathered, though any firm conclusions will require calculation of the interaction energy as a function of the geometry of the possible transition states.

With regard to our overall goal of the synthesis of nucleoside Q and its free base, α-halo ketones thus do not provide the correctly substituted pyrrolo[2,3-*d*]pyrimidines. Two possibilities exist which might allow entry into the 7-substituted 7-deazaguanine system. First, if α-halo aldehydes will condense with **3** to produce pyrrolo[2,3-*d*]pyrimidines with the same regiochemistry as the α-halo ketones, then the correct substitution pattern would be available. Second, it has been reported that 5,6-dimethyl-4-aminofuro[2,3-*d*]pyrimidine when refluxed with concentrated hydrochloric acid will partially rearrange via opening of the furo ring to 5,6-dimethyl-4-hydroxypyrrolo[2,3-*d*]pyrimidine.[39] Thus, the 5-substituted furo[2,3-*d*]pyrimidines of this study might rearrange to 5-substituted pyrrolo[2,3-*d*]pyrimidines. Both possibilities were investigated.

Though **6c** readily rearranged partially to **5c** upon heating in aqueous HCl, when a proton was present at C-6 of the furo[2,3-*d*]pyrimidine (**6a** and **6g**), only decomposition was observed, presumably due to the instability of the open-chain intermediate under the reaction conditions.

As a prototype aldehyde, 2-chloropropionaldehyde was investigated. In most solvents, including DMF, the results did not look promising. However, in Me_2SO at ambient temperature a smooth reaction occurred to give the 5-methylpyrrolo[2,3-*d*]pyrimidine **7** in 60% yield. **7** was clearly distinct from **5a** and its spectral data (see Table II and the Experimental Section) were also confirmatory. Thus, the regiospecificity of the reaction type was preserved (no **5a** was formed). While neither 2,3-dichloropropionaldehyde nor 2,3-dibromopropionaldehyde reacted with **3** to give a clean product (decomposition products were obtained prior to condensation), other aldehydes have also exhibited the same reactivity to afford only pyrrolo[2,3-*d*]pyrimidines. Research utilizing this observation toward a facile total synthesis of Q is in progress and will be reported in due course.

That condensation of **3** with various α-halo carbonyls leads to pyrrolo[2,3-*d*]pyrimidines and/or furo[2,3-*d*]pyrimidines is interesting from several standpoints. The literature on cyclizations with α-halo carbonyls provides some information useful in understanding the chemistry. As mentioned earlier, several electron-rich pyrimidines (aside from **3**) react with chloroacetaldehyde to produce pyrrolo[2,3-*d*]pyrimidines. 1-Methylcytosine[40] and 4-amino-2,6-dimethoxypyrimidine[28] react with chloroacetaldehyde and α-bromoacetophenone, respectively, to form imidazo[1,2-*c*]pyrimidines (**8** from 1-methylcytosine, for example). Neither 4,6-diaminopyrimidine



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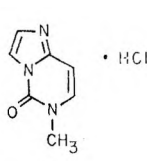

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nor 4-amino-6-pyrimidinone are reported to yield pyrrolo[2,3-*d*]pyrimidines with chloroacetaldehyde, though the nature of the products is not mentioned.[21] All of these data tend to indicate that there is a certain critical electron density (or HOMO coefficient) at C-5 which dictates whether cyclization will occur to that carbon or not, and **3** must exceed that minimum. The coupling of experimental observations with theoretical calculations might well provide a basis by which the direction (or directions) of cyclization of various pyrimidines with α-halo carbonyls could be predicted.[41]

Summary

The reaction of 2,6-diaminopyrimidin-4-one (**3**) with α-halo ketones proceeds via two distinct, regiospecific pathways, leading to 5-substituted and 5,6-disubstituted 2,4-diaminofuro[2,3-*d*]pyrimidines and/or 6-substituted and 5,6-disubstituted 2-aminopyrrolo[2,3-*d*]pyrimidin-4-ones. The former reaction provides a new and facile entry into the furo[2,3-*d*]pyrimidine system. The utilization of these 2,4-diaminofuropyrimidines and their derivatives as potential dihydrofolate reductase inhibitors (pteridine antagonists) has also been investigated and will be reported elsewhere. 2-Chloropropionaldehyde also reacts with **3** regiospecifically, forming only 2-amino-4-hydroxy-5-methylpyrrolo[2,3-*d*]pyrimidine (**7**). This observation allows convenient formation of the proper substitution pattern for nucleoside Q, and research toward its synthesis is currently in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer. ^{1}H NMR spectra were measured with Varian A-60A or EM-360 instruments, and ^{13}C NMR spectra with a Bruker WP 80; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Ultraviolet absorption spectra were recorded on a Cary 15 ultraviolet–visible spectrophotometer. Quantitative measurements were carried out by making a stock solution of the heterocycle in either H_2O (**5a, 5b, 6a, 6c, 6h, 7**) or CH_3OH (**5c–f, 6g**) and then diluting with either 0.1 N HCl, 0.1 N NaOH, pH 4.0 acetate buffer, or pH 7.0 phosphate buffer. Extinction coefficients are listed in parentheses. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. In all cases where analyses included methanol, the methyl protons were observed in the ^{1}H NMR spectra.

Reagent grade dimethylformamide was dried over molecular sieves and used directly. Dimethyl sulfoxide was distilled from calcium hydride.

Thin-layer chromatography was carried out on Eastman Chromagram sheets (silica gel) using the following systems: A, 9:1 $CHCl_3$–CH_3OH; B, 85:15 $CHCl_3$–CH_3OH; C, 4:1 $CHCl_3$–CH_3OH.

General Procedure for the Reaction of 2,6-Diaminopyrimidin-4-one (3) with α-Halo Ketones. To a suspension of **3** in DMF was added the α-halo ketone and the mixture was stirred (appropriate details are listed with each specific compound). The progress of the reactions was easily followed by TLC. Upon completion of the reaction, solvent was removed in vacuo. Purification was accomplished by column chromatography on silica gel.

2-Amino-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (5a) and 2,4-Diamino-5-methylfuro[2,3-*d*]pyrimidine (6a): 3 (0.5 g, 3.4 mmol), 1-chloro-2-propanone (**4a**, 0.37 g, 4 mmol), 6 mL of DMF; 50–60 °C; 2 days. Chromatography (2.5 × 38 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 300 mg of **5a** (55%, R_f 0.37, C) and 110 mg of **6a** (20%, R_f 0.56, C) as off-white solids. Recrystallization from methanol gave analytically pure materials. **5a** is initially isolated as the hydrochloride salt. Neutralization can be accomplished by stirring the salt 1 day at 80 °C with an excess of Amberlite IR-45 (OH^- form), followed by filtration and evaporation of solvent.

5a: mp (**5a**·HCl) >260 °C; ^{1}H NMR (**5a**·HCl, Me_2SO-d_6) δ 2.24 (s, 3, CH_3), 6.14 (s, 1, H_5), 6.6–9.0 (br m, 3, 3 NH), 11.66 (br s, 1, NHCO); ^{1}H NMR (**5a**, Me_2SO-d_6) δ 2.17 (s, 3, CH_3), 5.86 (s, 1, H_5), 6.27 (br s, 2, NH_2), 10.15 (br s, 1, NH), 10.80 (br s, 1, NH); MS *m/e* 164 (M^+, base), 163, 147, 135, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 222 (12 700), 264 (11 180); UV λ_{max} (pH 7.0) 217 (19 460), 260 (11 930), 280 (sh, 8050); UV λ_{max} (base) 260 (11 050).

Anal. Calcd for $C_7H_8N_4O$·HCl: C, 41.91; H, 4.52; N, 27.93. Found: C, 42.16; H, 4.81; N, 27.68.

6a: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.28 (s, 3, CH_3), 6.10 (br s, 2, NH_2), 6.60 (br s, 2, NH_2), 7.17 (s, 1, H_6); MS *m/e* 164 (M^+, base), 149, 135, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 257 (13 380), 302 (7390); UV λ_{max} (pH 7.0) 215 (11 150), 258 (12 020), 280 (sh, 7650); UV λ_{max} (base) 257 (12 040), 275 (sh, 8080).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 50.84; H, 4.95; N, 33.77.

2-Amino-6-carboethoxymethylpyrrolo[2,3-*d*]pyrimidin-4-one (5b): 3 (1.44 g, 10 mmol), ethyl 4-bromo-3-oxobutyrate (**4b**, 2.1 g, 10 mmol), 15 mL of DMF; 50 °C; 12 h. Chromatography (3.8 × 60 cm column, elution with 92:8 $CHCl_3$–CH_3OH) afforded 1.40 g (60%, R_f 0.70, C) of a colorless solid. Recrystallization from methanol gave analytically pure material: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.14 (t, 3, CH_3), 3.50 (s, 2, CH_2CO), 4.02 (q, 2, CH_2CH_3), 6.0 (s, 3, 2 NH, H_5), 10.12 (s, 1, NH), 10.80 (s, 1, NH); MS *m/e* 236 (M^+), 163 (base), 146, 121; exact mass calcd *m/e* 236.0909; found *m/e* 236.0915; UV λ_{max} (acid) 221 (14 440), 263 (12 020); UV λ_{max} (pH 7.0) 216 (18 530), 261 (13 730), 280 (sh, 9080); UV λ_{max} (base) 262 (11 500).

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.68; H, 5.20; N, 23.64.

2-Amino-5,6-dimethylpyrrolo[2,3-*d*]pyrimidin-4-one (5c) and 2,4-Diamino-5,6-dimethylfuro[2,3-*d*]pyrimidine (6c): 3 (4.0 g, 28 mmol), 3-bromo-2-butanone (**4c**, 5.0 g, 33 mmol), 15 mL of DMF; 55 °C; 1 day. Chromatography (5 × 80 cm, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.1 g of slightly yellow **6c** (42%, R_f 0.64, B) and 2.2 g of slightly pink **5c** (44%, R_f 0.48, B). Recrystallization of both compounds from methanol gave analytically pure material.

5c: mp 227–238 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 6, 2 CH_3), 4.8–6.7 (br s, 3, 3 NH), 11.6 (s, 1, NHCO); MS *m/e* 178 (M^+, base), 177, 163, 149, 125; exact mass calcd *m/e* 178.0855; found *m/e* 178.0858; UV λ_{max} (acid) 229 (14 040), 272 (9920); UV λ_{max} (pH 7.0) 223 (17 990), 266 (9810), 283 (sh, 7880); UV λ_{max} (base) 266 (9070).

Anal. Calcd for $C_8H_{10}N_4O$·CH_3OH: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.14; H, 6.67; N, 26.45.

6c: mp 175–185 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 2.16 (s, 3, CH_3), 3.8–5.5 (br s, 2, NH_2), 6.93 (br s, 2, NH_2); MS *m/e* 178 (M^+, base), 177, 163, 149, 135; exact mass calcd *m/e* 178.0855; found *m/e* 178.0858; UV λ_{max} (acid) 261 (14 830), 307 (7250); UV λ_{max} (pH 7.0) 259 (13 700), 280 (sh, 8580); UV λ_{max} (base) 259 (13 480).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.80; H, 5.74; N, 31.39.

2-Amino-5-methyl-6-phenylpyrrolo[2,3-*d*]pyrimidin-4-one (5d): 3 (2.90 g, 20 mmol), 2-bromo-1-phenyl-1-propanone (**4d**, 5.0 g, 23.5 mmol), 8 mL of DMF; 60 °C; 4 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.15 g of yellow **5d** (45%, R_f 0.49, A). Recrystallization from methanol provided analytically pure material: mp >260 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.40 (s, 3, CH_3), 6.09 (br s, 2, NH_2), 7.0–7.8 (m, 5, aromatic), 10.20 (br s, 1, NH), 11.08 (br s, 1, NHCO); MS *m/e* 240 (M^+, base), 239, 223, 206, 204; exact mass calcd *m/e* 240.1011; found *m/e* 240.1017; UV λ_{max} (acid) 230 (21 090), 290 (21 690); UV λ_{max} (pH 7.0) 227 (22 980), 297 (21 790); UV λ_{max} (base) 316 (22 000).

Anal. Calcd for $C_{13}H_{12}N_4O$·CH_3OH: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.69; H, 5.87; N, 20.83.

2-Amino-6-methyl-5-phenylpyrrolo[2,3-*d*]pyrimidin-4-one (5e): 3 (2.90 g, 20 mmol), 1-bromo-1-phenyl-2-propanone (**4e**, 4.30 g, 20 mmol), 20 mL of DMF; room temperature; 3 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 2.62 g of slightly violet-colored **5e** (54%, R_f 0.41, A). Recrystallization from methanol gave analytically pure material: mp >250 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 5.8–8.2 (br m, 8, aromatic, 3 NH), 11.14 (br s, 1, NHCO); MS *m/e* 240 (M^+, base), 239, 223, 205, 198; exact mass calcd *m/e* 240.1011; found *m/e* 240.1015; UV λ_{max} (acid) 235 (16 480), 254 (sh, 13 580), 275 (sh, 12 630); UV λ_{max} (pH 7.0) 234 (18 260), 264 (12 370), 297 (11 050); UV λ_{max} (base) 266 (11 800).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.01; H, 5.25; N, 23.39.

2-Amino-5-benzyl-6-methylpyrrolo[2,3-*d*]pyrimidin-4-one (5f): 3 (2.90 g, 20 mmol), 3-bromo-4-phenyl-2-butanone (**4f**, 4.50 g, 20 mmol), 20 mL of DMF; room temperature, 3 days. Chromatogra-

phy (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 1.90 g of white, crystalline **5f** (37%, R_f 0.38, A). Crystallization from methanol afforded analytically pure material: mp >250 °C; ^1H NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3), 3.88 (s, 2, CH_2), 5.90 (s, 2, NH_2), 6.9–7.2 (m, 5, aromatic), 9.90 (br s, 1, NH), 10.48 (br s, 1, NHCO); MS *m/e* 254 (M^+, base), 253, 239, 177, 163, 139; exact mass calcd *m/e* 254.1168; found *m/e* 254.1175; UV λ_{max} (acid) 229 (16 320), 269 (11 650); UV λ_{max} (pH 7.0) 223 (20 880), 266 (11 480), 286 (sh, 8780); UV λ_{max} (base) 267 (10 870).

Anal. Calcd for $C_{14}H_{14}N_4O$·CH_3OH: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.13; H, 6.22; N, 19.88.

5-Chloromethyl-2,4-diaminofuro[2,3-*d*]pyrimidine (6g): 3 (7.20 g, 50 mmol), 1,3-dichloroacetone (**4g**, 6.40 g, 50 mmol), 40 mL of DMF; room temperature; time 1 day. In this case filtration preceding removal of solvent under vacuum afforded 5.3 g of product. Chromatography of the residue from the filtrate (3.8 × 60 cm, elution with 9:1 $CHCl_3$–CH_3OH) afforded an additional 2.5 g of **6g**, total yield 78%, R_f 0.30, A. Recrystallization from methanol afforded analytically pure material: mp 178–188 °C dec; ^1H NMR (Me_2SO-d_6) δ 4.90 (s, 2, CH_2Cl), 6.12 (br s, 2, NH_2), 6.57 (br, s, 2, NH_2), 7.46 (s, 1, H_6); MS *m/e* 200, 198 (M^+, base), 163, 135, 121; exact mass calcd *m/e* 198.0308; found *m/e* 198.0312; UV λ_{max} (acid) 255 (10 420), 297 (5400); UV λ_{max} (pH 4.0) 259 (8560), 274 (sh, 6110); UV λ_{max} (pH 7.0) 215 (18 320), 278 (6590); UV λ_{max} (base) 259 (7440), 273 (sh, 6150).

Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21. Found: C, 42.24; H, 3.63; N, 28.15.

2,4-Diamino-5,6-tetramethylenefuro[2,3-*d*]pyrimidine (6h): 3 (2.90 g, 20 mmol), 2-chlorocyclohexanone (**4h**, 2.70 g, 20 mmol), 20 mL of DMF; 60 °C; 3 days. Chromatography (3.8 × 60 cm column, elution with 9:1 $CHCl_3$–CH_3OH) afforded 1.73 g (43%) of colorless crystals. Recrystallization from methanol gave analytically pure material: mp >250 °C; ^1H NMR (Me_2SO-d_6) δ 1.60 and 2.40 (2 m, 8, 4 CH_2), 4.5–6.0 (br s, 2, NH_2), 6.67 (br s, 2, NH_2); MS *m/e* 204 (M^+, base), 203, 176, 161; exact mass calcd *m/e* 204.1011; found *m/e* 204.1017; UV λ_{max} (acid) 217 (14 100), 265 (13 650); UV λ_{max} (pH 7.0) 216 (20 570), 265 (13 580); UV λ_{max} (base) 261 (10 190).

Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.76; H, 6.01; N, 27.25.

2-Amino-5-methylpyrrolo[2,3-*d*]pyrimidin-4-one (7). A solution of 4.50 g (30 mmol) of **3**, 0.74 g (8 mmol) of 2-chloropropanal, and 10 mg of K_2CO_3 in 20 mL of Me_2SO was stirred at room temperature. After 1 and 2 h, identical proportions of aldehyde and K_2CO_3 were added. After a total of 4 h, 3 mL of 58% NH_4OH was added and the mixture chromatographed on silica gel (3.8 × 50 cm, elution with 600 mL of CH_2Cl_2, then 2 L of 85:15 CH_2Cl_2–CH_3OH) to afford 2.37 g (60%) of off-white crystals. Recrystallization from methanol gave analytically pure material: mp 198–210 °C dec; ^1H NMR (Me_2SO-d_6) δ 2.14 (s, 3, CH_3), 5.97 (s, 2, NH_2), 6.30 (s, 1, H_6), 10.10 and 10.56 (2 s, 2, 2 NH); MS *m/e* 164 (M^+, base), 163, 147, 122; exact mass calcd *m/e* 164.0698; found *m/e* 164.0701; UV λ_{max} (acid) 227 (14 690), 265 (8540); UV λ_{max} (pH 7.0) 223 (18 460), 262 (9060), 276 (sh, 7050); UV λ_{max} (base) 262 (7970).

Anal. Calcd for $C_7H_8N_4O$·$0.8CH_3OH$: C, 49.36; H, 5.95; N, 29.52. Found: C, 49.16; H, 6.04; N, 29.73.

Registry No.—**3**, 56-06-4; **4a**, 78-95-5; **4b**, 13176-46-0; **4c**, 814-75-5; **4d**, 2114-00-3; **4e**, 23022-83-5; **4f**, 55985-68-7; **4g**, 534-07-6; **4h**, 822-87-7.

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Stereoselective Synthesis of 23-Deoxyantheridiol[1]

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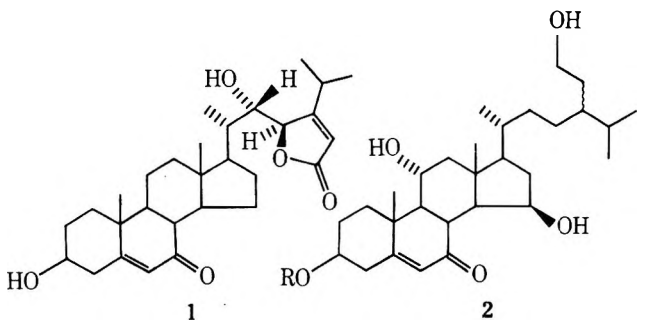
A highly stereoselective synthesis of (22*R*)-3β,22-dihydroxy-7-oxostigmasta-5,24(28)-dien-29-oic acid δ-lactone (23-deoxyantheridiol), a steroid produced by the aquatic fungus *Achlya*, has been achieved. Reaction of readily prepared 3β-acetoxycholesta-5,22(*E*)-dien-24-one with alkaline hydrogen peroxide gave almost exclusively the (22*S*,23*R*)-epoxide, which was converted to the (22*R*)-hydroxy-24-ketone with aluminum amalgam. The lactone ring was constructed by a novel intramolecular Wittig–Horner reaction. Esterification of the hydroxyl with bromoacetyl bromide followed by reaction with triethyl phosphite gave the phosphonate. Treatment of the phosphonate with sodium hydride yielded the unsaturated δ-lactone. The 7-ketone was introduced by photooxygenation followed by treatment with cupric acetate. 23-Deoxyantheridiol showed weak biological activity in *Achlya*.

The sexual reproductive process in *Achlya*, a widely distributed genus of saprophytic aquatic fungi, is initiated and coordinated by the steroid hormones antheridiol (**1**) and the oogoniols (**2**; R = H, $(CH_3)_2CHCO$, CH_3CH_2CO, or CH_3CO).[2,3]



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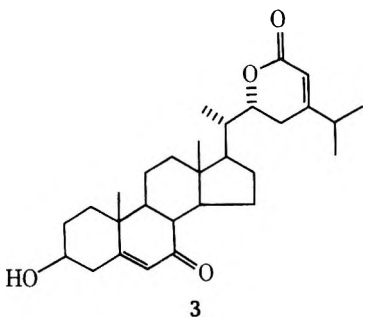


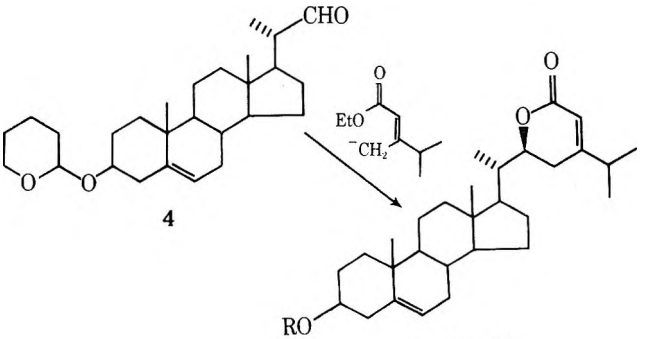
3

Antheridiol, which is secreted into the surrounding water by vegetative hyphae of female strains of the fungus, induces the formation of many antheridial branches or male sex organs on hyphae of male strains. The male is also stimulated to secrete the oogoniols which act on the female, causing the formation of oogonia or female sex organs. Developing oogonia are believed to secrete greater amounts of antheridiol than vegetative hyphae, and this results in chemotropic growth of the antheridial branches to the oogonia in order for conjugation of the sex organs to occur.[4]

Culture liquids of several female strains of *Achlya* have been found to contain antheridiol as well as the closely related steroid 23-deoxyantheridiol (**3**).[5] The structure of the latter steroid was confirmed by synthesis of its C-22 epimer by Green and Edwards some time ago.[5]

23-Deoxyantheridiol was slightly active in the induction of antheridial branches, but the activity was thought to be caused by traces of antheridiol. The two steroids possess similar mobilities on thin-layer chromatography, which was used for their isolation, so it was not possible to achieve complete separation of **1** from **3**. The synthetic C-22 epimer was found to be biologically inactive, but since correct stereochemistry at C-22 in antheridiol is important for full biological activity,[6] it seemed desirable to develop a synthetic route to **3** itself. We would then have sufficient amounts of pure natural product to make an accurate evaluation of its biological properties.

The synthetic method used by Green and Edwards involved aldol condensation of the tetrahydropyranyloxy derivative of 22,23-dinorchol-5-en-24-al (**4**) with the anion of ethyl *trans*-3,4-dimethyl-2-pentenoate, which gave the unsaturated lactone **5a**. Photooxygenation of **5a** followed by treatment with cupric acetate gave the corresponding 7-ketone **6**. Com-



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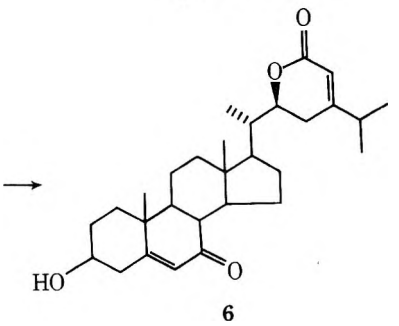
5a, R = H
b, R = Ac



6

parison of the spectral properties of the synthetic product with those of **3** showed that the two compounds were isomeric at C-22. Thus, aldol condensation with the aldehyde **4** gave almost exclusively a product having the 22*S* configuration. The stereochemical course of the reaction is similar to that reported for condensations involving related aldehydes, for example, in the synthesis of α-ecdysone[7] and antheridiol.[8]

It was therefore necessary to use a different approach to introduce an oxygen function at C-22 with the desired configuration. Sucrow and co-workers have demonstrated that epoxidation of 3β-acetoxy-27-nor-5α-cholesta-7,23(*E*)-dien-24-one with alkaline hydrogen peroxide is highly stereoselective. They were able to isolate in 85% yield the (22*S*,23*R*)-epoxide.[9] A similar result was reported by Popplestone and Unrau, who converted 3β-acetoxycholesta-5,22(*E*)-dien-24-one (**7**) to the (22*S*,23*R*)-epoxide **8** by reaction with alkaline hydrogen peroxide.[10] In the former case the configuration at C-22 was established by reduction with hy-

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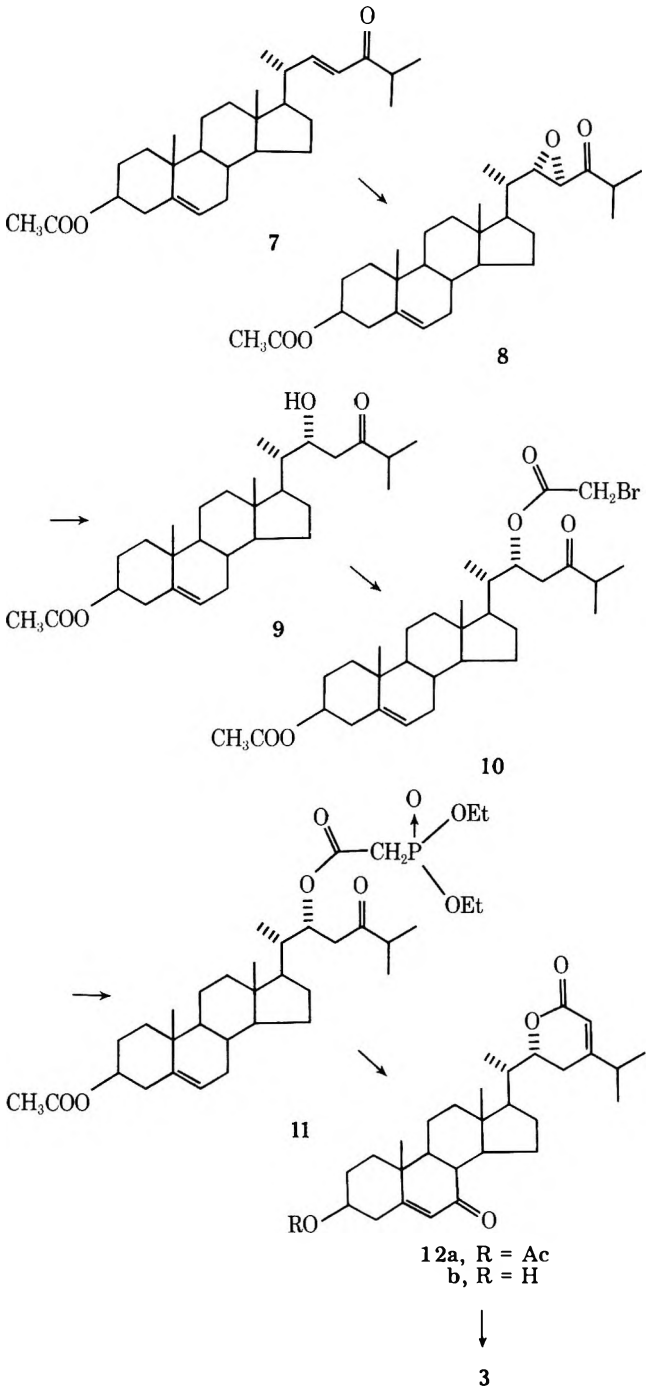

drazine to give (22*R*)-3β-acetoxy-27-nor-5α-cholesta-7,23(*E*)-dien-22-ol, which was then subjected to a Horeau analysis. The remarkable stereoselectivity of the epoxidation reaction may be due to a favored conformation of the side chain which results in one side of the double bond being less hindered than the other and therefore more susceptible to attack by hydroperoxide anion. However, examination of Dreiding models does not reveal any preferred conformation which would explain the observed stereoselectivity. It is interesting to note that the same stereoselectivity has been reported for the reaction of (22*E*)-6β-methoxy-3α,5-cyclo-5α-cholest-22-en-24-one with dimethyloxosulfonium methylide, which gave exclusively, and in high yield, the (22*S*,23*S*)-cyclopropyl ketone.[11] Reductive cleavage of the epoxide **8** would be expected to yield the hydroxy ketone **9** possessing the appropriate functionality for constructing a lactone ring with the same stereochemistry as that in **3**.

Wittig reaction of 3β-acetoxy-22,23-dinorchol-5-en-24-al[12] with the phosphorane prepared from 1-bromo-3-methylbutan-2-one, itself conveniently obtained by direct bromination of the corresponding ketone,[13] furnished the α,β-unsaturated ketone **7** in 87% yield. The latter was smoothly epoxidized with 30% hydrogen peroxide and dilute sodium hydroxide to give, after reacetylation of the product, a high yield (94%) of α,β-epoxy ketone. The NMR spectrum indicated that it was actually a mixture of **8** and the isomeric epoxide in a ratio of approximately 95:5. Attempts at reductive opening of the epoxide ring with chromium(II) acetate[14] gave some hydroxy ketone but also products from elimination (i.e., **7**) and possibly retro-aldol cleavage. However, reduction of **8** dissolved in ethanol–ether with aluminum amalgam gave an 86% yield of the desired hydroxy ketone **9**.[15]

We proposed to construct an unsaturated lactone ring on the side chain of **9** by reaction with the anion of triethyl phosphonoacetate. In another investigation it had been found that 1-hydroxy-2-methylpentan-3-one reacted readily with the anion of triethyl phosphonoacetate to give 4-ethyl-5-methyloxacyclohex-3-en-2-one in moderate yield.[16] However, when the condensation was attempted with **9**, an extensive retro-aldol reaction occurred giving back the starting aldehyde which then reacted with phosphonoacetate anion.

The C-22 hydroxyl in **9** was therefore protected by esterification with bromoacetyl bromide and pyridine, and the bromo ester **10** was heated with triethyl phosphite to give the phosphonate **11** in an overall yield of 75%. Intramolecular condensation occurred readily when sodium hydride was added to a solution of **11** in tetrahydrofuran and the mixture heated. A good yield (86%) of the unsaturated δ-lactone **12a** was thus obtained. Attempts were also made to obtain **12a** from the triphenylphosphonium salt instead of the phosphonate, but the Wittig reaction failed, possibly for steric reasons. Reformatsky reaction of the bromo ester **10** also failed to yield any condensation product. Although the intramolecular Wittig–Horner reaction has been used for the construction of butenolides,[17] to our knowledge this is the first successful application to the preparation of unsaturated δ-lactones such as **12a**.

Completion of the synthesis involved hydrolysis of the acetate group of **12a** with dilute potassium carbonate solution in methanol to give the corresponding alcohol **12b**. Photooxygenation of the latter in pyridine solution with hematoporphyrin as a sensitizer afforded the 5α-hydroperoxide, which was converted to **3** by treatment with cupric acetate in pyridine. The overall yield for the synthesis starting from a readily available aldehyde, 3β-acetoxy-22,23-dinorchol-5-en-24-al, was about 30%.

The properties of synthetic 23-deoxyantheridiol were the same as those which have been reported for the natural product. Further confirmation of the structure was obtained by comparing the synthetic compound with its C-22 epimer prepared according to the method of Green and Edwards.[5] The NMR spectra of the two compounds show distinct differences as reported earlier. The H-22 signal in the spectrum of **3** appears as a doublet of triplets centered at δ 4.38 (J = 12 and 4.5 Hz), while that in the epimer occurs as a doublet of doublets at δ 4.40 (J = 13 and 4 Hz). The doublet for H-21 is fully visible (at δ 1.05) in the spectrum of the epimer **6**, but only the high-field arm of the doublet for H-21 (centered at δ 1.03) is observed in the spectrum of **3**. The low-field arm is hidden by one of the isopropyl hydrogen signals at δ 1.06.

Measurement of the CD curves indicated the difference in stereochemistry of the lactone rings in **5b** and **12a**, the former giving a negative Cotton effect at 254 nm and the latter a positive Cotton effect at 251 nm.

Fourier transform ^{13}C NMR spectra of steroids belonging to the natural and unnatural stereochemical groups were also recorded. It was possible to make definite spectral assignments for virtually all of the carbons in each of the compounds by the use of off-resonance decoupled spectra and by comparison

Table I. ^{13}C NMR Chemical Shifts (ppm Relative to Me_4Si) in 23-Deoxyantheridiol (3) and a Related Series of Steroids[a]

carbon	12a	12b	3	5b	5a	6
1	37.0	37.3	36.4	37.0	37.3	36.4
2	27.8	31.6	31.1	27.8	31.6	31.1
3	73.9	71.7	70.3	73.9	71.6	70.4
4	38.1	42.3	41.9	38.1	42.2	41.8
5	139.8	140.9	165.8	139.7	140.9	165.5
6	122.4	121.4	125.7	122.5	121.4	126.1
7	31.9	31.9	201.6	32.0[b]	32.0[b]	201.7
8	31.9	31.9	45.4	31.9[b]	31.8[b]	45.4
9	50.1	50.2	49.6[b]	49.9	50.0	49.8[b]
10	36.6	36.5	38.4	36.6	36.5	38.2
11	21.0	21.1	21.2	21.0	21.1	21.3
12	39.7	39.8	38.7	39.7	39.6	38.6
13	42.9	42.9	43.5	42.3	42.2	43.1
14	56.3	56.4	49.9[b]	56.4	56.4	50.0[b]
15	24.3	24.3	26.3	24.2	24.2	26.2
16	27.4	27.4	27.7	27.8	27.7	28.2
17	52.3	52.3	51.1	51.4	51.4	50.2[b]
18	11.8	11.8	11.9	11.8	11.7	11.8
19	19.3	19.4	17.3	19.3	19.4	17.4
20	38.9	38.9	38.7	39.7	39.6	39.8
21	13.4	13.5	13.6	13.3	13.2	13.4
22	79.9	79.9	79.9	79.6	79.6	79.6
23	25.2	25.2	25.1	29.6	29.6	29.7
24	166.6	166.3	166.8	166.8	167.0	166.9
25	34.8	34.8	34.8	34.7	34.7	34.7
26	19.9	19.9	19.9	19.9	19.8	19.9
27	20.4	20.4	20.4	20.4	20.4	20.4
28	113.6	113.5	113.4	113.5	113.4	113.4
29	166.2	166.2	166.3	166.2	166.4	166.3
CH_3 (acetate)	21.4			21.4		
C=O (acetate)	170.4			170.4		

[a] ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$. The concentrations of the solutions ranged from 0.05 to 0.2 M. Spectral parameters were the following: acquisition time, 1 s; pulse delay, 0.3 s; number of transients, 8–60 K; data points, ~8000. [b] Assignments may be reversed in vertical column.

with literature data.[18] The assignments are given in Table I. They indicate that the carbons most affected by a change in stereochemistry at C-22 are C-23 and to a lesser extent C-20 and C-17. These results are in accord with expectation.[19]

Synthetic 23-deoxyantheridiol has been tested for biological activity and found to be weakly active. The lowest concentration of **3** which induced significant antheridial branch formation was approximately 50 ng/mL. This is more than one thousand times greater than the minimum concentration of antheridiol required for biological activity. Thus, it appears that 23-deoxyantheridiol is not needed by the organism, at least not for the induction of antheridial hyphae. At present one can only speculate about the function of **3**. It could possibly be a metabolite or, perhaps more likely, a biosynthetic precursor of antheridiol. Its structure indicates that it might be formed from the trienoic acid **13**, which has been shown to be a precursor of antheridiol.[20] Ring closure in the trienoic acid would give the δ-lactone in **3**, and oxidation at C-7 would complete its biosynthesis. If reopening of the lactone ring can occur in the cell, then **3** could be a potential precursor of antheridiol. There is also a possibility that **3** may be involved in some other stage of the sexual process in *Achlya*. We plan to investigate these possibilities.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Spectra were obtained on the following instruments: Varian EM 390 (^1H NMR), Varian CFT 20 (^{13}C NMR), Perkin-Elmer 550 spectrophotometer (UV), Beckman IR 18A-X (IR), LKB 9000 (mass spectra), and a Cary 61 circular dichrometer coupled with a Texas Instruments 980A computer. NMR results are reported in parts per million (or δ) using Me_4Si as an internal standard (δ = 0). The ionizing voltage for mass spectra was 70 eV. Infrared spectra were taken of KBr pellets unless otherwise specified. Elemental analyses were performed by Pascher Laboratories, Bonn, W. Germany.

Isobutyrylmethylenetriphenylphosphorane.[21] Method A. To a stirred suspension of methyltriphenylphosphonium iodide (16.15 g, 40 mmol) in dry ether (250 mL) under argon was added a solution of phenyllithium in benzene–ether (17 mL, 2.4 M). The resulting yellow-orange mixture was stirred for 2 h and cooled in an ice bath. To it was added a solution of isobutyryl bromide (2.1 mL) in dry ether (50 mL) during 15 min. After stirring overnight, the mixture was filtered through a sintered glass funnel. The residue was mixed thoroughly with chloroform and the insoluble material discarded. The chloroform solution was washed with 5% HCl and 5% NaOH (3 × 40 mL), dried ($MgSO_4$), and evaporated to yield a yellow oil. NMR analysis showed this oil to be a mixture of the desired phosphorane and a methyltriphenylphosphonium halide. The oil was vigorously stirred with three portions of hot benzene to separate the soluble phosphorane and the insoluble phosphonium salt. The benzene solutions were decanted, combined, and evaporated to yield the crystalline phosphorane (4.90 g, 72%). The original ether layer yielded additional product if dilute HCl (1–2 mL) was added and the mixture was shaken for 5 min and then filtered to isolate the salt of the phosphorane. This could be converted to the phosphorane by dissolving in chloroform, shaking with dilute NaOH (excess), and removing the chloroform. Crystallization from ethyl acetate gave pure phosphorane: mp 172–175 °C; NMR ($CDCl_3$) δ 1.15 (d, J = 7 Hz, $(CH_3)_2C$), 2.50 (m, J = 7 Hz, CH), 3.66 (broad d, J = 27 Hz, P=CH), 7.5 (m, 15 aromatic H).

Method B. Bromine (12.8 mL) was added in one portion to a stirred solution of methyl isopropyl ketone (21.5 g) in dry methanol (250 mL). After the solution became colorless (ca. 20 min), $NaHCO_3$ (21 g) in H_2O (250 mL) was added carefully and the mixture was stirred until most of the bubbling had stopped. The solution was extracted with hexane (3 × 170 mL), and the hexane extracts were combined, washed with dilute $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated in a stream of nitrogen. The resulting liquid was distilled to yield a fraction (17.1 g) boiling at 72–82 °C (25 mm) that was shown by NMR analysis to be a mixture of 1-bromo-3-methylbutan-2-one (93%) and 3-bromo-3-methylbutan-2-one (7%).[13] The mixture of bromo ketones (17.1 g) in dry benzene (75 mL) was added to a solution of triphenylphosphine (29.0 g) in a minimum of dry benzene. After standing for 17 h, the mixture was filtered and the white crystals were washed several times with hot benzene. This phosphonium salt [31.2 g; NMR ($CDCl_3$) δ 1.11 (d, J = 7.5 Hz, $(CH_3)_2C$), 3.26 (m, J = 7.5 Hz, CH), 5.90 (d, J = 12 Hz, P–CH_2), 7.8 (m, 15 aromatic H)] was dissolved in chloroform, and the solution was shaken well with 10% NaOH (75 mL). The chloroform layer was separated, washed with H_2O, dried ($MgSO_4$), and evaporated to yield 24.26 g (30% overall yield from methyl isopropyl ketone) of crystalline phosphorane.

3β-Acetoxycholesta-5,22(*E*)-dien-24-one (7). This compound was prepared from the condensation of 3β-acetoxy-22,23-dinorcholenaldehyde[12] and isobutyrylmethylenetriphenylphosphorane in 87% yield according to the procedure of Fryberg et al.:[21] mp 138–140 °C; NMR ($CDCl_3$) δ 0.72 (s, 3, H-18), 1.02 (s, 3, H-19), 1.10 (d, 9, J = 7 Hz, H-21, H-26, and H-27), 2.02 (s, 3, OAc), 2.80 (m, 1, J = 7 Hz, H-25), 4.6 (broad m, 1, H-3), 5.36 (m, 1, H-6), 6.03 (d, 1, J = 16 Hz, H-23), 6.70 (d of d, 1, J = 8.5 and 16 Hz, H-22); IR 2940, 1740, 1700, 1630, 1250, 1040 cm^{-1}.

(22*S*,23*R*)-3β-Acetoxy-24-oxocholest-5-ene 22,23-Epoxide (8). To a stirred warm solution (35 °C water bath) of unsaturated ketone **7** (253 mg) in absolute ethanol (16 mL) was added quickly 30% hydrogen peroxide (1.05 mL) and 4 N NaOH (0.55 mL). The warm water bath was removed after 1 h and the mixture stirred for an additional hour. The solvent was partially removed (~40%) in a nitrogen stream, and the mixture was extracted twice with ether. The ether extracts were combined, washed with water and brine, dried ($MgSO_4$), and evaporated to yield a clear oil. NMR analysis of the crude product showed it to be a mixture of **8** and the corresponding 3β-alcohol. Acetylation of the mixture with acetic anhydride and pyridine yielded the epoxide **8** (0.24 g, 94%): mp 125–126 °C; NMR ($CDCl_3$) δ 0.68 (s, 3, H-18), 1.01 (s, 3, H-19), 1.03, 1.06, 1.11, 1.14 (H-21, H-26, and H-27), 2.01 (s, 3, OAc), 2.80 (m, 1, H-22), 3.25 (d, 0.95, J = 2 Hz, H-23, (22*S*,23*R*)-epoxide), 3.36 (d, 0.05, J = 2 Hz, H-23, (22*R*,23*S*)-epoxide), 4.60 (broad m, 1, H-3), 5.36 (m, 1, H-6); IR (CH_2Cl_2) 1730 cm^{-1}.

(22*R*)-3β-Acetoxy-24-oxocholest-5-en-22-ol (9). To the epoxy ketone **8** (2.95 g) dissolved in dry ether (125 mL) and absolute ethanol (60 mL) was added Al(Hg) (made from 4.6 g of Al foil)[22] and 5 drops

of H_2O. The mixture was stirred vigorously for 4 h and suction filtered, and the residue was washed with ether. The combined ether filtrates were washed with water and brine and dried ($MgSO_4$), and the solvent was evaporated to yield a crystalline solid (2.84 g). Recrystallization from methanol afforded **9** as white plates (2.55 g, 86%): mp 142–144 °C; NMR ($CDCl_3$) δ 0.73 (s, 3, H-18), 0.93 (d, 3, J = 7 Hz, H-21), 1.03 (s, 3, 19-H), 1.12 (d, 6, J = 7 Hz, H-26 and H-27), 2.00 (s, 3, OAc), 4.06 (m, 1, 22-H), 4.56 (broad m, 1, H-3), 5.30 (m, 1, H-6); IR 3530, 2980, 1742, 1700, 1255, 1045 cm^{-1}; MS m/e 398 (27, M^+ − HOAc), 380 (17), 312 (100).

(22*R*)-3β-Acetoxy-22-(bromoacetoxy)cholest-5-en-24-one (10). The ketol **9** (740 mg) was dissolved in dry ether (30 mL) and dry pyridine (162 mg). This stirred solution was cooled in an ice bath, and bromoacetyl bromide (400 mg) in ether (3 mL) was added dropwise during 5 min. A white precipitate formed during the addition. The ice bath was removed after 10 min and the mixture stirred for 12 h. Thin-layer chromatography showed some starting material still present, so more pyridine (0.25 mL) was added. After stirring 3 h more, the mixture was suction filtered and the residue washed with ether. The combined ether filtrates were washed twice with 10% HCl, H_2O, and brine, dried ($MgSO_4$), and evaporated to yield a crystalline solid (875 mg). Recrystallization from methanol afforded **10** (800 mg, 86%) as white plates. A second recrystallization from methanol gave pure **10**: mp 154–156 °C; NMR ($CDCl_3$) δ 0.70 (s, 3, H-18), 0.97 (d, 3, J = 7 Hz, H-21; only high-field arm visible), 1.00 (s, 3, H-19), 1.08 (d, 6, J = 7 Hz, H-26 and H-27), 2.00 (s, 3, OAc), 3.75 (s, 2, $C(=O)CH_2Br$), 4.6 (broad m, 1, H-3), 5.36 (m, 1, H-6), 5.43 (m, 1, H-22); IR 2950, 1760, 1740, 1720, 1295, 1257 cm^{-1}; MS m/e 520 (0.8, M^+ − HOAc), 518, 379 (1.3, M^+ − HOAc − $HOOCCH_2Br$), 43 (100).

(22*R*)-3β-Acetoxy-22-(diethylphosphonoacetoxy)cholest-5-en-24-one (11). The bromoacetate **10** (1.09 g) was heated with excess triethyl phosphite (4 mL) in an oil bath (130 °C) for 3 h. A stream of nitrogen was used to blow off the excess triethyl phosphite, leaving a clear oil which crystallized on standing. Recrystallization from hexane yielded **11** (1.05 g, 88%) as white needles: mp 117.5–119 °C; NMR ($CDCl_3$) δ 0.70 (s, 3, H-18), 0.96 (d, 3, J = 7 Hz, H-21; only high-field arm visible), 1.02 (s, 3, H-19), 1.08 (d, J = 7 Hz, H-26 and H-27), 1.33 (t, 6, J = 7.5 Hz, $P(OC-CH_3)_2$), 2.02 (s, 3, OAc), 2.89 (d, 2, J = 21 Hz, CH_2–P), 4.16 (m, 4, J = 7.5 Hz, $P(O-CH_2C)_2$), 4.6 (broad m, 1, H-3), 5.36 (m, 1, H-6), 5.43 (m, 1, H-22); IR 2940, 1735, 1720, 1245, 1025 cm^{-1}; MS m/e 576 (1.2, M^+ − HOAc), 440 (1.4, M^+ − $C_6H_{13}O_5P$), 380 (100, M^+ − HOAc − $C_6H_{13}O_5P$).

(22*R*)-3β-Acetoxy-22-hydroxystigmasta-5,24(28)-dien-29-oic Acid δ-Lactone (12a). To a stirred solution of phosphonate **11** (507 mg) in dry tetrahydrofuran (25 mL) was added 57% NaH (34 mg). After stirring for 5 min at room temperature and 1 h at reflux, the solution was cooled and diluted with H_2O, and the solvent volume was reduced in a stream of nitrogen. The resulting suspension was extracted with ether. The ether extract was washed twice with water and brine, dried ($MgSO_4$), and evaporated to leave a clear oil (405 mg). Chromatography on silica gel with dichloromethane–petroleum ether yielded **12a** (330 mg, 86%) and **7** (28 mg, 8%). Crystallization from hexane–methanol afforded **12a** as white needles: mp 163.5–165 °C; NMR ($CDCl_3$) δ 0.73 (s, 3, H-18), 1.02 (s, 3, H-19), 1.03 (d, 3, J = 6 Hz, H-21), 1.10 (d, 6, J = 7 Hz, H-26 and H-27), 2.02 (s, 3, OAc), 4.40 (d of t, 1, J = 12 and 4.5 Hz, H-22), 4.60 (broad m, 1, H-3), 5.39 (m, 1, H-6), 5.78 (broad s, 1, H-28); IR 2940, 1739, 1718, 1640, 1245 cm^{-1}; MS m/e 482 (0.3, M^+), 422 (27, M^+ − HOAc), 43 (100); CD (c ca. 0.0005 g/mL, CH_3OH) $[\theta]_{300}$ +160, $[\theta]_{290}$ +740, $[\theta]_{280}$ +3160, $[\theta]_{270}$ +9260, $[\theta]_{260}$ +18 390, $[\theta]_{251}$ max +23 090, $[\theta]_{250}$ +22 720, $[\theta]_{240}$ +12 960, $[\theta]_{230}$ +410, $[\theta]_{220}$ +6810.

(22*R*)-3β,22-Dihydroxystigmasta-5,24(28)-dien-29-oic Acid δ-Lactone (12b). To a stirred solution of **12a** (290 mg) in tetrahydrofuran (3 mL) and methanol (40 mL) was added a 10% K_2CO_3 solution (60% CH_3OH, 40% H_2O; 1 mL). After stirring for 23 h, 10% NH_4Cl (1.5 mL) and H_2O (30 mL) were added and the volume was reduced by ca. 50% in a stream of nitrogen. Filtration afforded **12b** (243 mg, 92%). Crystallization from ethyl acetate–chloroform yielded white needles: mp 260–263 °C; NMR ($CDCl_3$) δ 0.72 (s, 3, H-18), 1.00 (s, 3, H-19), 1.02 (d, 3, J = 6 Hz, H-21; only high-field arm visible), 1.10 (d, 6, J = 7 Hz, H-26 and H-27), 3.52 (broad m, 1, H-3), 4.37 (d of t, 1, J = 12 and 4.5 Hz, H-22), 5.35 (m, 1, H-6), 5.77 (broad s, 1, H-28); IR 3500, 2930, 1711, 1640, 1065 cm^{-1}; MS m/e 440 (21, M^+), 422 (32, M^+ − H_2O), 407 (19, M^+ − H_2O − CH_3), 139 (100).

(22*R*)-3β,22-Dihydroxy-7-oxostigmasta-5,24(28)-dien-29-oic Acid δ-Lactone (3). A stirred solution of **12b** (137 mg) in dry pyridine (14 mL) containing hematoporphyrin (15 mg) was irradiated with four 15-W fluorescent lamps for 39 h, during which time oxygen was bubbled through the solution. The reaction mixture was diluted with ether, treated with charcoal, and filtered through Celite, and the ether was blown off. $Cu(OAc)_2 \cdot H_2O$ (115 mg) was added to the pyridine solution, and the mixture was stirred for 8 h. After dilution with ethyl acetate, the solution was washed with dilute phosphoric acid, dilute $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated. Chromatography of the crude product on silica gel with dichloromethane–methanol yielded **3** (100 mg, 70%), mp 260–264 °C. An analytical sample was prepared by preparative LC (Waters Model M-6000A; μ Porasil; hexane–dichloromethane–methanol, 30:10:1; 4.2 mL/min; 5000 psi; followed by crystallization from ethyl acetate): mp 268–270 °C; NMR ($CDCl_3$) δ 0.72 (s, 3, H-18), 1.03 (d, 3, J = 6 Hz, H-21), 1.10 (d, 6, J = 7 Hz, H-26 and H-27), 1.20 (s, 3, H-19), 3.6 (broad m, 1, H-3), 4.38 (d of t, 1, J = 12 and 4.5 Hz, H-22), 5.67 (s, 1, H-6), 5.73 (broad s, 1, H-28); IR 3470, 2940, 1705, 1675, 1635 cm^{-1}; MS m/e 454 (90, M^+), 436 (34, M^+ − H_2O), 316 (66, M^+ + H-lactone), 245 (100, $C_{16}H_{21}O_2$); UV λ_{max} (CH_3OH) 226 nm (ε 18 800); CD (c ca. 0.0006 g/mL, CH_3OH) $[\theta]_{300}$ +0, $[\theta]_{290}$ +970, $[\theta]_{280}$ +5700, $[\theta]_{270}$ +12 000, $[\theta]_{260}$ +19 000, $[\theta]_{256}$ max +21 900, $[\theta]_{250}$ +17 500, $[\theta]_{240}$ −670, $[\theta]_{230}$ −34 000, $[\theta]_{220}$ −65 300.

Anal. Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.30; H, 9.20.

(22*S*)-3β,22-Dihydroxystigmasta-5,24(28)-dien-29-oic Acid δ-Lactone (5a). This compound was prepared essentially by the procedure of Green et al.[5] except for a few modifications. 3β-Acetoxy-22,23-dinorcholenaldehyde was used rather than **4**. Workup and column chromatography gave **5a** directly (35%) and **5b** (48%). **5b** could be converted to **5a** following the procedure previously described for the 22*R* isomer. **5a** had the following properties: mp 220–222 °C; NMR ($CDCl_3$) δ 0.70 (s, 3, H-18), 1.00 (s, 3, H-19), 1.10 (d, 6, J = 7 Hz, H-26 and H-27), 3.53 (broad m, 1, H-3), 4.40 (d of d, 1, J = 13.5 and 3 Hz, H-22), 5.33 (m, 1, H-6), 5.73 (broad s, 1, H-28); IR 3450, 2945, 1721, 1645, 1265 cm^{-1}; MS m/e 440 (14, M^+), 422 (27, M^+ − H_2O), 407 (11, M^+ − H_2O − CH_3), 139 (100).

5b had the following properties: mp 210–212 °C; NMR ($CDCl_3$) δ 0.70 (s, 3, H-18), 1.00 (s, 3, H-19), 1.07 (d, 6, J = 7 Hz, H-26 and H-27), 2.01 (s, 3, OAc), 4.40 (d of d, 1, J = 13.5 and 3 Hz, H-22), 4.60 (broad m, 1, H-3), 5.35 (m, 1, H-6), 5.75 (broad s, 1, H-28); IR 2940, 1734, 1721, 1645, 1260 cm^{-1}; MS m/e 482 (0.4, M^+), 422 (100, M^+ − HOAc); CD (c ca. 0.0006 g/mL, CH_3OH) $[\theta]_{300}$ −290, $[\theta]_{290}$ −8700, $[\theta]_{280}$ −12 100, $[\theta]_{270}$ −16 200, $[\theta]_{260}$ −25 400, $[\theta]_{254}$ max −28 500, $[\theta]_{250}$ −25 400, $[\theta]_{240}$ −6700, $[\theta]_{230}$ +11 200, $[\theta]_{220}$ +2500.

5b and its C-22 epimer, **12a**, were found to have quite different mobilities when subjected to LC (Waters Model M-6000A, μ Porasil; hexane–dichloromethane–methanol, 30:10:1; 4.2 mL/min; 5000 psi). **12a** was eluted with a retention time of 4.9 min, while **5b** was eluted with a retention time of 5.6 min. On coinjection baseline separation was evident.

A sample of **12a** prepared from recrystallized bromoacetate **10** and phosphonate **11** showed no **5b** (<1%) on LC. But in a sample of **12a** prepared without recrystallizing **10** and **11**, a small amount of **5b** (~5%) could be detected.

A sample of **5b** prepared by the method of Green et al.[5] showed a peak with the same retention time as **12a** (~2%) on LC.

Biological assays were carried out according to the method of Barksdale et al.[6]

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Registry No.—**3**, 32212-69-4; **5a**, 32212-70-7; **5b**, 67237-33-6; **6**, 32212-71-8; **7**, 32230-64-1; **8**, 42261-08-5; **9**, 67237-34-7; **10**, 67237-35-8; **11**, 67237-36-9; **12a**, 67237-30-3; **12b**, 67237-31-4; isobutyrylmethylenetriphenylphosphorane, 19753-67-4; methyltriphenylphosphonium iodide, 2065-66-9; isobutyryl bromide, 2736-37-0; methyl isopropyl ketone, 563-80-4; 1-bromo-3-methylbutan-2-one, 19967-55-6; 3-bromo-3-methylbutan-2-one, 2648-71-7; triphenylphosphine, 603-35-0; 3β-acetoxy-22,23-dinorcholenaldehyde, 10211-88-8; bromoacetyl bromide, 598-21-0; triethyl phosphite, 122-52-1.

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Studies on the Synthesis of Cardiotonic Steroids. 4.[1] Synthesis of Strophanthidin

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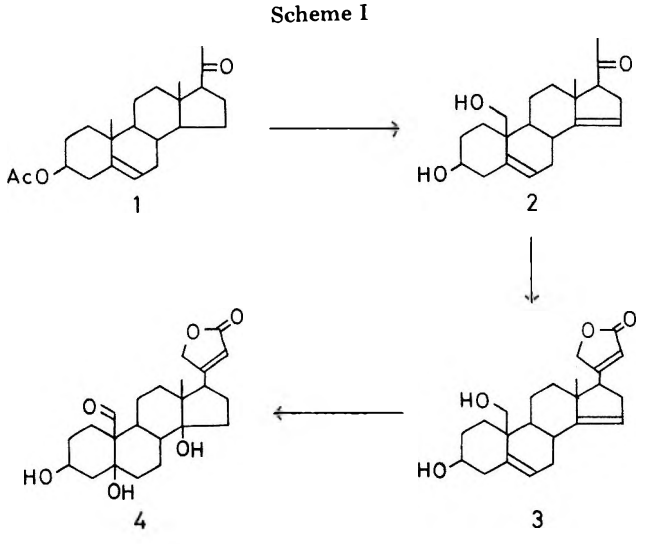
The synthesis of strophanthidin (4) starting with pregnenolone acetate (1) is described. 19-Hydroxylation and introduction of a 14 double bond afforded 9, which was then transformed into the cardatrienolide 13. By stepwise introduction of 5β- and 14β-hydroxy groups, strophanthidol (22) was obtained. Conversion of strophanthidol to strophanthidin was successfully carried out by the oxidation with chromic trioxide in hexamethylphosphoric triamide.

Since Sondheimer's first synthesis of digitoxigenin in 1962,[2] there have been recorded the syntheses of several other natural cardenolides—periplogenin,[3a,4] xysmalogenin,[3b] uzarigenin,[3c,4] and canarigenin.[3d,4] However, the synthesis of more complex 19-oxygenated cardenolides represented by strophanthidin (4)[5] has not been accomplished, seemingly due to the difficulty in assembling unstable functionalities on the steroid nucleus.[6] We now describe the synthesis of strophanthidin, starting with readily available pregnenolone acetate (1).

Our synthetic approach to strophanthidin involved the following principal phases of conversion (Scheme I): (1) derivation of a 19-hydroxy group and a 14 double bond from 1 leading to the dihydroxydienone 2, (2) transformation of 2 to the cardatrienolide 3 without affecting functional groups in the steroid skeleton, (3) formation of two tertiary β-hydroxy groups at the 5 and 14 positions, followed by selective oxidation of the 19-hydroxymethyl moiety to an aldehyde group.

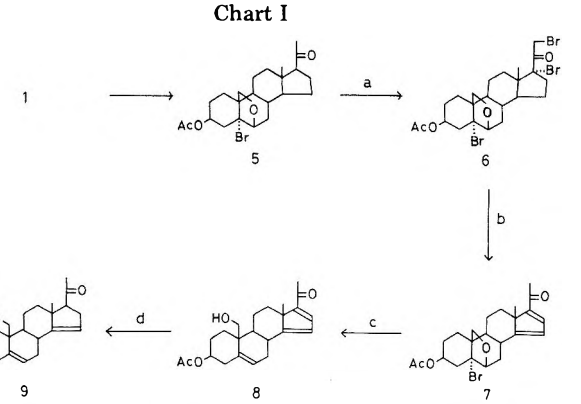
Scheme I



Preparation of the 3-acetate of the dihydroxy ketone 2 is outlined in Chart I. 5-Bromo-6,19-oxidopregnenolone acetate (5) prepared from pregnenolone acetate (1) by an established method[7] was brominated with 2 equiv of bromine to give the 17,21-dibromo compound 6 in 63% yield. It was then subjected to lithium bromide catalyzed dehydrobromination in *N*,*N*-dimethylformamide[8] to furnish the conjugated dienone 7 in 70% yield. Treatment of 7 with zinc dust in weakly acidic 2-propanol at reflux temperature generated the 5 double bond,[7a] yielding the trienone 8 in 89% yield. Selective hydrogenation of the 16 double bond of 8 leading to the dienone 9 was accomplished in 82% yield by heating with triphenylstannane in toluene, a convenient method for the partial reduction of conjugated dienones developed in our laboratory.[9]

The next task—construction of the cardatrienolide structure 13—was then performed by the reaction sequence (Chart II) which had been developed during our digitoxigenin synthesis.[9] First, the 21-methylthio derivative 10 was obtained in 44% yield by the base-catalyzed reaction of 9 with diethyl oxalate followed by the reaction of the resulting 21-oxalyl derivative with methyl thiotosylate in the presence of excess

Chart I



[a] Br_2, AcOH. [b] LiBr, DMF. [c] Zn, *i*-PrOH–AcOH. [d] Ph_3SnH, PhMe.

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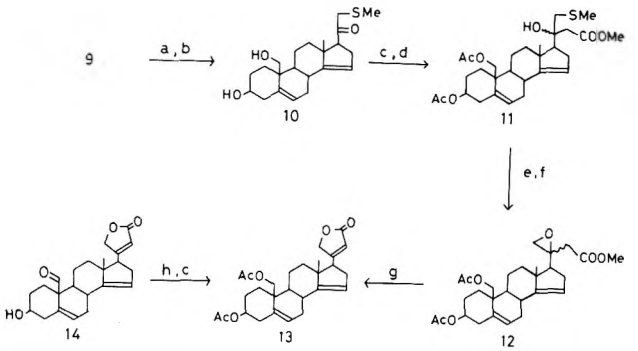
Chart II



[a] $(COOEt)_2$, MeOK. [b] TsSMe, AcOK. [c] Ac_2O, pyr. [d] $BrCH_2COOMe$, Zn. [e] $Me_3{}^+OBF_4{}^-$. [f] 0.5 N NaOH, CH_2Cl_2. [g] Alumina. [h] $NaBH_4$.

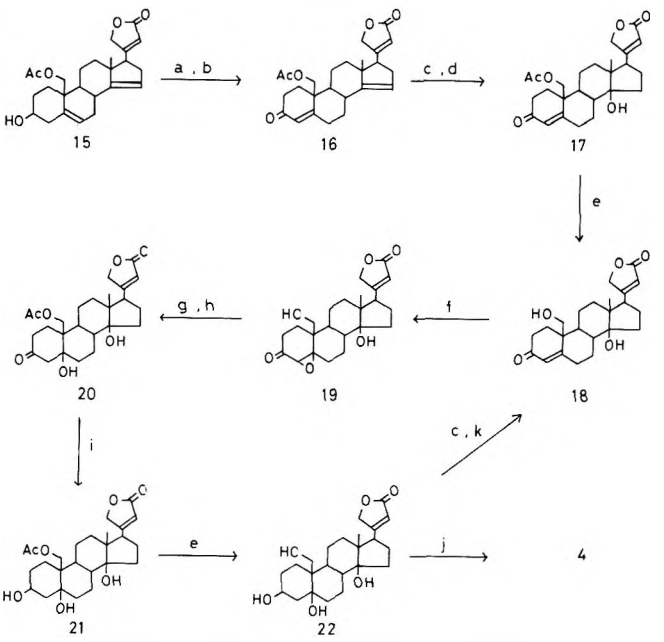
potassium acetate in ethanol.[8a] Reaction of the diacetate of ketone **10** with methyl bromoacetate and zinc dust in boiling benzene for a short period gave the Reformatsky product (**11**) as a mixture of 20-epimers. Treatment of **11** with an equivalent amount of trimethyloxonium tetrafluoroborate in nitromethane at room temperature gave the corresponding methylsulfonium salt, which was stirred in dichloromethane with dilute sodium hydroxide to produce the β,γ-epoxy ester **12**. The latter compound was then absorbed on an alumina column, and after 1 to 5 h the column was eluted to furnish anhydropachygenol diacetate (**13**).[10] The steps from **11** to **13** were carried out without purification of the intermediates in an overall yield of 61%. The structure of **13** was confirmed by comparisons of the spectral data and TLC with those of an authentic sample prepared from dianhydrostrophanthidin (**14**)[11] by sodium borohydride reduction followed by acetylation.

With the synthesis of the cardatrienolide **13** in hand, effort was directed to the introduction of two tertiary and β-oriented hydroxyl groups at the 5 and 14 positions (Chart III). Selective hydrolysis of **13** under weakly basic condition produced the 19-monoacetate **15**, which, on chromic acid oxidation and subsequent treatment of the product with oxalic acid, afforded the conjugated ketone **16** in 60% yield.

Now, according to an established procedure[12] for the introduction of the 14β-hydroxy group, **16** was subjected to the addition of hypobromous acid with aqueous *N*-bromoacetamide followed by hydrogenolysis of the intermediate bromohydrin with Raney Ni to give a bromine-free product. Although TLC of the product showed a single spot under a variety of solvent systems, MS clearly indicated that it was a mixture of two components showing two molecular ion peaks—*m/e* 428 ($C_{25}H_{32}O_6$) ascribable to the desired product **17** and *m/e* 426 ($C_{25}H_{30}O_6$). The byproduct having two hydrogen atoms less than the 14β-hydroxy cardenolide **17** could not be the 14,15-epoxide, since in the NMR spectrum no peak due to 15-hydrogen was observed; nor could it be the 15-ketone,[13] since the intense peak observed in the MS at *m/e* 408 ($M^+ - H_2O$) was not compatible with that structure. Based on these facts, the structure of an 8(14)-en-15-ol was tentatively assigned to the $C_{25}H_{30}O_6$ product.[14] Although the mixture was resolved by high-pressure liquid chromatography, revealing an ca. 75% content of **17**, isolation of **17** was successfully carried out by oxidative destruction of the by product with Jones reagent followed by preparative TLC. The 14β-hydroxy compound **17** thus obtained in 72% yield was identical with an authentic sample[15] prepared from strophanthidol (**22**) (comparisons of spectral data and TLC). Hydrolysis of the 19-acetate group by potassium bicarbonate afforded the 19-hydroxy compound **18** in almost quantitative yield.

The reaction of **18** with cold alkaline hydrogen peroxide proceeded smoothly to give the 4β,5β-epoxide **19** in 87% yield.

Chart III



[a] Cr(VI). [b] $(COOH)_2$. [c] AcNHBr, H_2O. [d] Raney Ni. [e] $KHCO_3$. [f] H_2O_2, NaOH. [g] Ac_2O, pyr. [h] $Cr(OAc)_2$. [i] Urushibara Ni A. [j] CrO_3, $(Me_2N)_3PO$. [k] AcOH, Δ.

The β orientation of the epoxy group expected from the literature precedents[16] was firmly supported by the circular dichroism which showed a positive Cotton effect.[17] Reductive cleavage of the epoxide ring was then carried out on the 19-acetate of **19** by treatment with chromium(II) acetate in ethanol. The product consisted of an easily separable mixture of the β-hydroxy ketone **20**[15a] and of the conjugated ketone **17** (ca. 1:1). Treatment of **20** with Urushibara nickel A[18] in refluxing ethanol provided strophanthidol 19-acetate (**21**). Strophanthidol (**22**) was obtained by saponification of **21** with potassium bicarbonate at room temperature. The identity of the synthetic and natural specimens was proved by comparisons of spectral data and TLC.

The final step in our strophanthidin synthesis consisted in the selective oxidation of the 19-hydroxy group of strophanthidol. Literature precedents concerned with the oxidation of strophanthidol and related systems indicate that chromic acid,[19a] *N*-haloamide[19a,b] and PtO_2[15b,19c] all favor the oxidation of the secondary 3-hydroxy group in preference to the 19-primary alcohol. In our hands also, oxidation with both pyridinium chlorochromate[20] and sulfur trioxide–pyridine–dimethyl sulfoxide[21] proceeded in the same fashion, and therefore the protection of the 3-hydroxy group seemed to be essential.[19a] Fortunately, we found, however, that chromic trioxide in hexamethylphosphoric triamide[22] was an excellent reagent for this particular oxidation. Although the rate of the oxidation was very slow, strophanthidin was obtained in good yield, no ketonic product being noticed. The synthetic and natural specimens of strophanthidin were completely identical in IR, NMR, MS, and TLC behavior.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Jeol PMX-60 or a Varian EM-390 instrument. Chemical shifts are reported in units δ (ppm) from internal tetramethylsilane. Infrared spectra were taken on a Jasco IRA-1 spectrometer and ultraviolet spectra on a Hitachi 124 instrument. Mass spectral data were obtained on a Jeol JMS-01SG-2 instrument at an ionization potential of 75 eV. Optical rotations were measured on a Jasco DIP-4 automatic polarimeter, and circular dichroism spectra were recorded on a Jasco J-20 spectrometer. Combustion analyses were carried out at the Microanalytical Laboratory of this

university. Dry argon was used in reactions requiring an inert atmosphere. Most reactions were followed by thin-layer chromatography over Merck precoated silica gel plates. Preparative TLC was carried out on Merck silica gel (0.06–0.20 mm). High-pressure liquid chromatography was performed on a Toyo Soda HLC-803 instrument.

3β-Acetoxy-6β,19-oxido-5α,17α,21-tribromopregnan-20-one (6). A solution of 5.43 g of bromine in 200 mL of acetic acid was added slowly to a stirred solution of 7.44 g of 5[7a] in 75 mL of acetic acid at 40–45 °C over a period of 1 h. After consumption of bromine was complete, the pale yellow solution was poured into ice–water. The white precipitate was filtered, washed well with water, and dried. The crude product (8.95 g) was crystallized from acetone–methanol to give 6.31 g of **6**, mp 172.5–175.5 °C, which was contaminated with a trace amount of impurities as evidenced by TLC (probably 5,17-dibromide and 5,17,21,21-tetrabromide) and was used for the next step without further purification. An analytical sample was obtained by chromatography over silica gel (elutions with benzene–ether) followed by recrystallization from acetone as colorless needles: mp 178–179 °C; $[\alpha]^{27}_D$ −8.0° (*c* 0.68, $CHCl_3$); IR (KBr) 1730, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (s, 18-H), 2.07 (s, OAc), 3.86 (AB q, *J* = 10, 32 Hz, 19-H), 4.34 (AB q, *J* = 14, 32 Hz, 21-H), 5.20 (m, 3-H).

Anal. Calcd for $C_{23}H_{31}O_4Br_3$: C, 45.20; H, 5.11. Found: C, 45.43; H, 5.28.

3β-Acetoxy-5α-bromo-6β,19-oxidopregna-14,16-dien-20-one (7). To a solution of 6.95 g of **6** in 55 mL of dry *N*,*N*-dimethylformamide was added 2.72 g of anhydrous lithium bromide, and the mixture was stirred and heated at 90–95 °C under an Ar atmosphere. After 4 h the dark brown reaction mixture was poured into water. The precipitate was filtered, washed with water, and dried. The crude product (4.55 g) was dissolved in 150 mL of hot ether, decolorized with active charcoal, and concentrated to a small volume. The pale yellow crystals of the dienone **7** which had separated were collected, mp 169–171 °C (3.53 g). An analytical sample was obtained by chromatography over silica gel (elutions with benzene–ether) and crystallization from ether as prisms: mp 174–175 °C; $[\alpha]^{27}_D$ +297.6° (*c* 0.39, $CHCl_3$); IR (KBr) 1735, 1640, 1520 cm^{-1}; UV λ_{max} (MeOH) 206 (ε 6430) and 306 nm (12 800); NMR (CCl_4) δ 1.20 (s, 18-H), 1.98 (s, OAc), 2.25 (s, 21-H), 3.89 (AB q, *J* = 9, 12 Hz, 19-H), 4.09 (d, *J* = 5 Hz, 6-H), 5.07 (m, 3-H), 5.95 (br d, *J* = 3 Hz, 15-H), 7.08 (d, *J* = 3 Hz, 16-H); MS *m/E* (rel abundance) 448, 450 (M^+, 8), 369 (19), 309 (100).

Anal. Calcd for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.50. Found: C, 61.45; H, 6.30.

3β-Acetoxy-19-hydroxypregna-5,14,16-trien-20-one (8). To a solution of 3.36 g of **7** in 200 mL of 2-propanol was added 1.84 g of zinc dust and 1 mL of acetic acid. The mixture was stirred and heated under reflux for 5.5 h. After cooling to room temperature, it was filtered and evaporated in vacuo. The residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$), and evaporated. The residual crystalline mass was recrystallized from methanol–dichloromethane to give 2.47 g of **8**: mp 236–237.5 °C; $[\alpha]^{27}_D$ +305.3° (c 0.38, $CHCl_3$); IR (KBr) 3490, 1730, 1710, 1640, 1520 cm^{-1}; UV λ_{max} (MeOH) 206.5 (ε 6950), 310 nm (11 150); NMR ($CDCl_3$) δ 1.23 (s, 18-H), 2.02 (s, OAc), 2.32 (s, 21-H), 3.87 (AB q, *J* = 10, 21 Hz, 19-H), 4.60 (m, 3-H), 5.87 (br s, 6-H), 5.97 (t, *J* = 3 Hz, 15-H), 7.20 (d, *J* = 3 Hz, 16-H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.34; H, 8.31.

3β-Acetoxy-19-hydroxypregna-5,14-dien-20-one (9). To a solution of 3.7 g of triphenylstannane in 40 mL of toluene was added 2.18 g of **8** and few milligrams of azobis(isobutyronitrile) and the mixture was heated under reflux with occasional additions of the radical initiator (1–2-h interval). After 10 h (disappearance of **8** on TLC, chloroform–ethyl acetate, 10:3), the solution was allowed to cool and the precipitate of white crystals of hexaphenylditin was removed by filtration. The filtrate was evaporated in vacuo and the residual viscous oil was subjected to silica gel chromatography (elutions with benzene–chloroform). Crystalline fractions showing a single spot on TLC were collected (1.79 g, mp 148–152 °C) and recrystallized from isopropyl ether to give 1.45 g of **9**: mp 154–155 °C; $[\alpha]^{27}_D$ −9.5° (*c* 0.53, $CHCl_3$); IR (KBr) 3410, 1730, 1695 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 18-H), 2.07 (s, OAc), 2.20 (s, 21-H), 4.60 (m, 3-H), 5.15 (m, 15-H), 5.80 (m, 6-H); MS *m/e* (rel abundance) 372 (M^+, 14), 312 (82), 294 (30), 281 (100).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.19; H, 8.80.

3β,19-Dihydroxy-21-methylthiopregna-5,14-dien-20-one (10). Potassium methoxide was prepared in 30 mL of dry benzene by the reaction of 0.90 mL of dry methanol with 4.0 g of 22.7% KH (mineral oil was removed by washing with benzene) under an Ar atmosphere. To the resulting suspension were added 1.56 g of diethyl oxalate and 2.02 g of **9** in 20 mL of benzene, and the mixture was stirred overnight at room temperature. After the addition of 2 M NaH_2PO_4, the organic product was isolated by extraction with a mixture of ether–methanol and dried in vacuo over P_2O_5. The crude 21-oxalyl derivative obtained was dissolved in 40 mL of dry ethanol followed by the addition of 1.32 g of methyl thiotosylate and 3.20 g of anhydrous potassium acetate. The solution was then heated at 60 °C for 8 h, cooled, mixed with 10 mL of 10% KOH, and stirred for 1.5 h at room temperature. The mixture was diluted with ether, and the organic solution was washed with water, dried ($MgSO_4$), and evaporated to give 885 mg of **10** as a pale yellow solid (mp 154–158 °C; essentially one spot on TLC, ethyl acetate–chloroform, 1:1) which without further purification was employed for the next step. An analytical sample was obtained by silica gel chromatography (elutions with chloroform–ethyl acetate, 3:7) followed by crystallization from isopropyl ether–methanol: mp 159–160 °C; IR (KBr) 3400, 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 18-H), 2.08 (s, SMe), 3.20 (br s, 21-H), 3.70 (AB q, *J* = 12, 18 Hz, 19-H), 5.12 (m, 15-H), 5.75 (m, 6-H); MS *m/e* (rel abundance) 376 (M^+, 68), 358 (32), 346 (36), 239 (100).

Anal. Calcd for $C_{22}H_{32}O_3S$: C, 70.18; H, 8.57. Found: C, 70.02; H, 8.74.

The diacetate of **10** (not crystallizable) was obtained by the usual procedure employing acetic anhydride and pyridine: IR (film) 1735, 1700 cm^{-1}; NMR (CCl_4) δ 0.87 (s, 18-H), 1.93 (s, OAc), 2.00 (s, SMe), 3.01 (br s, 21-H), 4.15 (AB q, *J* = 12, 36 Hz, 19-H), 5.10 (m, 15-H), 5.60 (m, 6-H); MS *m/e* 460 (M^+), 400, 340, 251.

Methyl 3β,19-Diacetoxy-20-hydroxy-21-methylthio-24-norchola-5,14-dienoate (11). To a solution of 730 mg of the diacetate of compound **10** in 25 mL of dry benzene was added 0.5 mL of methyl bromoacetate and 124 mg of freshly activated zinc dust. The mixture was heated with stirring and the solvent was slowly distilled. When ca. 15 mL of benzene was removed, vigorous reaction occurred. After continued heating and stirring for 10 min, the homogeneous reaction mixture was cooled, washed with dilute HCl and water, dried ($MgSO_4$), and evaporated. The residual viscous oil was chromatographed over silica gel (30 g), eluting with mixtures of chloroform–benzene to give 280 mg of **11** as a pale yellow gum which could not be induced to crystallize and was shown by spectral data to be a mixture of 21-epimers: NMR (CCl_4) δ 1.13 (s, 18-H), 2.00 (br s, OAc), 2.08, 2.12 (s, SMe), 2.60, 2.72 (br s, 21-H), 3.67 (hr s, COOMe), 4.18 (AB q, *J* = 12, 34 Hz, 19-H), 4.47 (br m, 3-H), 5.12 (m, 15-H), 5.63 (m, 6-H); MS *m/e* 534 (M^+), 516, 503, 473, 460, 413, 400, 353, 340, 251.

3β,19-Diacetoxycarda-5,14,20(22)-trienolide (13). (A) From 11. A solution of 207 mg of **11** in 2 mL of nitromethane was treated with 64 mg of trimethyloxonium tetrafluoroborate at room temperature. After 40 min the solvent was evaporated in vacuo at 20–25 °C. The residual *S*-methyl compound was dissolved in 7 mL of dichloromethane and the solution was vigorously stirred with 7 mL of 0.5 N NaOH at room temperature for 1 h. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. The gummy β,γ-epoxy ester (**12**) which on TLC (benzene–ethyl acetate, 10:1) showed two partially overlapping spots originating from 20-epimers was dissolved in a small volume of benzene and charged on an alumina column (basic, activity II, 27 g). After 5 h the column was eluted with benzene–ether (5:1) to give 108 mg of crystalline product (**13**), which showed a single spot on TLC. Recrystallization from methanol produced white needles: mp 193–194.5 °C; $[\alpha]^{22}_D$ −92.9° (c 1.32, $CHCl_3$); IR (KBr) 1785 (sh), 1740, 1625 cm^{-1}; UV λ_{max} (MeOH) 217 nm (ε 12 700); NMR ($CDCl_3$) δ 0.86 (s, 18-H), 2.05 (s, OAc), 4.28 (AB q, *J* = 12, 54 Hz, 19-H), 4.78 (br s, 21-H), 5.30 (m, 15-H), 5.72 (m, 6-H), 5.92 (br s, 22-H); MS *m/e* 454 (M^+), 394, 334, 321, 319. The spectral data were completely identical with those of an authentic sample (below).

Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.61; H, 7.73.

(B) From Dianhydrostrophanthidin (14). To a solution of 90 mg of 14[11] in 4.5 mL of 80% dioxane was added 32 mg of sodium borohydride in 3 mL of 80% dioxane. After 2 h at room temperature, the mixture was acidified by the addition of 4 N H_2SO_4 and diluted with water. The white precipitate was collected and crystallized from acetone to give a quantitative yield of the 3,19-diol (anhydropachygenol),[10] mp 240–243 °C.

The diacetate **13** was obtained by the usual manner as white needles: mp 194.5–196 °C; $[\alpha]^{22}_D$ −99.2° (*c* 1.32, $CHCl_3$).

Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.38; H, 7.32.

19-Acetoxy-3β-hydroxycarda-5,14,20(22)-trienolide (15). To a solution of 86 mg of the diacetate **13** in 8.6 mL of methanol was added 0.2 mL of 2 M $KHCO_3$ and the mixture was stirred for 14 h at

room temperature. Extraction with chloroform and crystallization of the product from methanol afforded 44 mg of **15** as white needles: mp 212–215 °C; IR (KBr) 3460, 1778, 1745, 1695, 1623 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (s, 18-H), 2.03 (s, OAc), 3.5 (br m, 3-H), 4.20 (AB q, J = 12, 34 Hz, 19-H), 4.71 (br s, 21-H), 5.20 (m, 15-H), 5.60 (m, 6-H), 5.85 (br s, 22-H).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.80; H, 8.05.

19-Acetoxy-3-oxocarda-4,14,20(22)-trienolide (16). To a stirred suspension of 62 mg of pyridinium chlorochromate in 0.5 mL of dichloromethane was added 78 mg of **15** in 2 mL of dichloromethane. Usual workup of the reaction mixture afforded a resinous material, which was then treated with 1 mL of 1% ethanolic oxalic acid at 70 °C for 2 h. The mixture was extracted with chloroform, washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residual pale yellow gum was subjected to preparative TLC (chloroform–methanol, 100:3), affording 47 mg of crystals which on recrystallization from acetone gave 45 mg of **16** as prisms: mp 181.5–183 °C; IR (KBr) 1780, 1750, 1735, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (s, 18-H), 2.02 (s, OAc), 4.40 (AB q, J = 11, 33 Hz, 19-H), 4.75 (br s, 21-H), 5.29 (m, 15-H), 5.91 (br s, 4-H and 22-H); MS m/e 410 (M^+), 350.

Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.15; H, 7.31.

19-Acetoxy-14β-hydroxy-3-oxocarda-4,20(22)-dienolide (17). To a stirred solution of 90 mg of **16** in 3.6 mL of acetone was added 0.3 mL of water, 37 mg of N-bromoacetamide, and 90 μL of 70% $HClO_4$ at 0 °C. After continued stirring and cooling for 20 min, the reaction mixture was treated with 5% $Na_2S_2O_3$ and extracted with dichloromethane. The organic solution was washed with cold brine, dried ($MgSO_4$), and evaporated in vacuo at room temperature. The pale yellow resinous residue (essentially homogeneous to TLC, chloroform–methanol, 25:1) was then dissolved in a mixture of 7 mL of methanol and 7 mL of dichloromethane, and the solution was added to a suspension of ca. 3 g of Raney Ni (W-4, H_2 saturated at 2 atm) in 20 mL of methanol containing an acetate buffer for controlling pH at 6.7. The suspension was stirred for 2 h at 20 °C, filtered, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated to give 90 mg of a semicrystalline residue. Although TLC showed the product to be essentially homogeneous (chloroform–methanol, 20:1), MS and high-pressure liquid chromatography (4 mm × 30 cm, Toyo Soda LS-410 ODS packing, MeOH) indicated that it was a mixture of two products (ca. 3:1), **17** (major product) and presumably the compound having the 8(14)-en-15-ol structure: MS (obtained by subtraction of the peaks due to **17** from those of the mixture) m/e (rel abundance) 426 (M^+, 11), 408 (100), 366 (17), 348 (38). A 20-mg portion of the mixture was titrated with Jones reagent in acetone at 0 °C. The product isolated by chloroform extraction was then subjected to preparative TLC (chloroform–methanol, 20:1) to give **17** (15 mg) which was crystallized from ethanol as prisms: mp 189–190 °C (lit.[15a] mp 185–187 °C, lit.[15b] mp 186–187 °C); $[\alpha]^{27}_D$ +118.2° (c 0.18, MeOH) (lit.[15b] +101°); UV λ_{max} (MeOH) 227 nm (ϵ 24 200);[15a] IR (KBr) 3500, 1780, 1755 (sh), 1740, 1660, 1615 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 18-H), 2.01 (s, OAc), 4.37 (AB q, J = 12, 32 Hz, 19-H), 4.87 (br s, 21-H), 5.89 (br s, 4-H and 22-H); MS m/e (rel abundance) 428 (M^+, 96), 410 (12), 408 (24), 368 (61), 356 (65), 350 (37), 245 (35), 215 (100).

Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.81; H, 7.55.

14β,19-Dihydroxy-3-oxocarda-4,20(22)-dienolide (18). (A) From 17. To a solution of 10 mg of **17** in 1 mL of methanol was added 30 μL of 2 M $KHCO_3$, and the solution was stirred at room temperature for 48 hr. Extraction of the mixture with chloroform followed by drying ($MgSO_4$) and evaporation of the solvent afforded 9.2 mg of **18**, mp 248–251 °C, from acetone–ether (lit.[15b] mp 247–251 °C, lit.[19c] mp 232–240 °C): NMR ($CDCl_3$) δ 0.93 (s, 18-H), 3.98 (br s, 19-H), 4.90 (br s, 21-H), 5.90 (br s, 4-H and 22-H); MS m/e (rel abundance) 386 (M^+, 5), 368 (40), 356 (30), 350 (18), 338 (100).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.24; H, 7.59.

(B) From Strophanthidol (22). To a solution of 500 mg of **22**[23,24] in 12.5 mL of *tert*-butyl alcohol was added 2.5 mL of water and 207 mg of N-bromoacetamide. The mixture was kept in the dark and at 20 °C overnight. After decolorization by the addition of 10% $Na_2S_2O_3$ and dilution with 15 mL of water, the solution was extracted thoroughly with chloroform. The organic layers were washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in 10 mL of acetic acid, and the solution was refluxed for 18 min. After dilution with 5 mL of water, the solution was concentrated in vacuo and extracted with chloroform. The chloroform solution was washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. On trituration of the residue with acetone, 494 mg of a pale yellow solid was obtained and recrystallized from acetone–ether: mp 251–252 °C; $[\alpha]^{27}_D$ +83.6° (c 0.79, MeOH) (lit.[15b] +91°); UV λ_{max} (MeOH) 222 nm (ϵ 22 700);[15b] IR (KBr) 3500, 3430, 1780, 1740, 1650–1630 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.58; H, 7.79.

14β,19-Dihydroxy-4β,5β-epoxy-3-oxocard-20(22)-enolide (19). To a solution of 203 mg of 18 in 20 mL of methanol was added 0.30 mL of 2 N NaOH and 0.75 mL of 30% H_2O_2 at 0 °C, and the homogeneous mixture was stirred at 0 °C for 1 h. Another 0.10 mL of 2 N NaOH and 0.25 mL of 30% H_2O_2 were added, and the solution was stirred for 45 min at 0 °C. The solution was neutralized by the addition of acetic acid, diluted with 10 mL of water, and extracted thoroughly with chloroform. The extracts were washed with aqueous $FeSO_4$, 5% $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The residual gum (178 mg) which was essentially homogeneous to TLC was crystallized from methanol to give 142 mg of **19** as white needles; mp 198–200 °C; IR (KBr) 3560, 3410, 3320, 1735, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 18-H), 2.93 (s, 4-H), 3.93 (AB q, J = 11, 23 Hz, 19-H), 4.90 (br s, 21-H), 5.90 (br s, 22-H); CD (c 0.006, MeOH) $[\theta]_{345}$ 0, $[\theta]_{302}$ +13 020, $[\theta]_{263}$ +2000, $[\theta]_{236}$ +11 340, $[\theta]_{225}$ +6040.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.90; H, 7.44.

The acetate of **19** was obtained by the usual procedure employing acetic anhydride and pyridine as an amorphous solid: NMR ($CDCl_3$) δ 0.91 (s, 18-H), 2.13 (s, OAc), 2.91 (s, 4-H), 4.37 (AB q, J = 11, 24 Hz, 19-H), 4.87 (br s, 21-H), 5.85 (br s, 22-H).

19-Acetoxy-5β,14β-dihydroxy-3-oxocard-20(22)-enolide (20). To a stirred suspension of freshly prepared chromous acetate (from 0.3 g of $CrCl_3 \cdot 6H_2O$)[25] in 1 mL of ethanol was added 70 mg of the 19-acetate of **19** in 7.5 mL of ethanol under an Ar atmosphere. After 30 min, the mixture was filtered, and the filtrate was evaporated in vacuo and extracted with chloroform. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 69 mg of a mixture of the enone **17** and the desired product **20** (ca. 1:1 by NMR). Preparative TLC (chloroform–methanol, 8:1) afforded 32 mg of **20** (not crystallizable):[15a] IR (film) 3480, 1740, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (s, 18-H), 2.07 (s, OAc), 4.40 (s, 19-H), 4.85 (br s, 21-H), 5.84 (br s, 22-H).

Strophanthidol 19-Acetate (21). To a solution of 15 mg of **20** in 1 mL of ethanol was added an excess amount of freshly prepared Urushibara nickel A,[18] and the mixture was refluxed gently with stirring. After 1.5 h the mixture was filtered and evaporated. Preparative TLC (ethyl acetate) of the residue afforded 0.5 mg of **17** and 7.5 mg of strophanthidol 19-acetate (**21**). The latter product was crystallized from aqueous acetone as prisms: mp 136–139 °C (lit.[15a] mp 136–139 °C, lit.[23] mp 134–136 °C); $[\alpha]^{27}_D$ +35.7° (c 0.75, EtOH) (lit.[15a] +34.8°); IR (KBr) 3380, 1780, 1750, 1710, 1615 cm^{-1}; NMR ($CDCl_3$) δ 0.84 (s, 18-H), 2.08 (s, OAc), 4.15 (m, 3-H), 4.39 (br s, 19-H), 4.86 (br s, 21-H), 5.84 (br s, 22-H). The spectral data and TLC were identical with those of an authentic sample prepared by monoacetylation of strophanthidol (**22**) according to literature.[15a,23]

Strophanthidol (22). To a solution of 10 mg of strophanthidol 19-acetate (**21**) in 1 mL of methanol was added 20 μL of 2 M $KHCO_3$, and the homogeneous mixture was stirred at room temperature for 20 h. The mixture was diluted with 50 mL of chloroform, and the organic layer was washed with a small amount of water and brine, dried ($MgSO_4$), and evaporated. The residue (one spot on TLC, chloroform–methanol, 10:1) was recrystallized three times from acetone–ether to give 4.5 mg of **22** as granules: mp 138–140 °C (lit.[19c] mp 138–142/152/222 °C, lit.[24] mp 136–140 °C); $[\alpha]^{27}_D$ +38.4° (c 0.26, MeOH) (lit.[24] +36.9°); IR (KBr) 3400, 1780, 1750–1740, 1620 cm^{-1}; MS m/e (rel abundance) 402 (M^+, 100), 384 (14), 372 (17), 368 (22), 354 (17). IR, MS and TLC were completely identical with those of an authentic sample prepared by sodium borohydride reduction of strophanthidin.[23,24]

Strophanthidin (4). To 0.2 mL of hexamethylphosphoric triamide was added 60 mg of chromic trioxide, and the mixture was stirred for 1 h at room temperature to give a homogeneous solution. A solution of 40.6 mg of strophanthidol (**22**) in 0.4 mL of hexamethylphosphoric triamide was then added and the stirring was continued for 24 h. The reaction mixture was extracted with ethyl acetate, and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to preparative TLC (chloroform–methanol, 9:1) to give 13 mg of strophanthidin (**4**) and 1 mg of unreacted **22**. Strophanthidin was recrystallized from aqueous methanol as white needles: mp 221.5–223.5 °C, mmp 215–217 °C with Merck strophanthidin (mp 208–212 °C, $[\alpha]_D$ +45.4°); $[\alpha]^{27}_D$ + 42.2° (c 0.15, MeOH); UV λ_{max} (MeOH) 217 nm (ϵ 15 500); NMR ($CDCl_3$) δ 0.86 (s, 18-H), 4.16 (m,

3-H), 4.85 (br s, 21-H), 5.84 (br s, 22-H), 9.93 (s, CHO); MS *m/e* (rel abundance) 404 (M^+, 1), 386 (3), 358 (23), 340 (100), 322 (63).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.21; H, 7.71.

Registry No.—**4**, 66-28-4; **5**, 41767-48-0; **6**, 67270-86-4; **7**, 67270-87-5; **8**, 67270-88-6; **9**, 67270-89-7; **9** 21-oxalyl derivative, 67270-90-0; **10**, 67270-91-1; **10** diacetate, 67270-92-2; **11** isomer 1, 67270-93-3; **11** isomer 2, 67335-50-6; **12** isomer 1, 67270-94-4; **12** isomer 2, 67335-51-7; **13**, 67270-95-5; **14**, 6785-67-7; **15**, 67270-96-6; **16**, 67270-97-7; **17**, 19667-18-6; **18**, 3566-40-3; **19**, 67270-98-8; **19** 19-acetate derivative, 67270-99-9; **20**, 67335-52-8; **21**, 17162-14-0; **22**, 560-54-3; methyl thiotosylate, 4973-66-4; methyl bromoacetate, 96-32-2; diethyl oxalate, 95-92-1.

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Dibenzocyclooctadiene Antileukemic Lignan Synthesis. (±)-Steganone[1]

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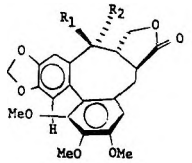
A new route to the unsaturated oxo ester **16**, an intermediate in the Raphael synthesis of steganone (**4**) and its companion antileukemic lignans steganacin (**1**) and steganangin (**2**), is described. Key reactions utilized in the synthetic sequence were photochemical ring closure of a stilbenecarboxylic acid to a phenanthrene, the trimethylsilyl azide modification of the Curtius rearrangement of carboxylic acids, and a two-carbon ring expansion of a 9-phenanthrylamine with dimethyl acetylenedicarboxylate.

Kupchan[2] has reported the isolation and structural determination of the dibenzocyclooctadiene lignan lactones[3] **1**–**4** from an alcoholic extract of *Steganotaenia araliacea* Hochst. Because of the significant[2] antileukemic activity reported for steganacin **1** and steganangin **2** (the *O*-acetyl and *O*-angelyl



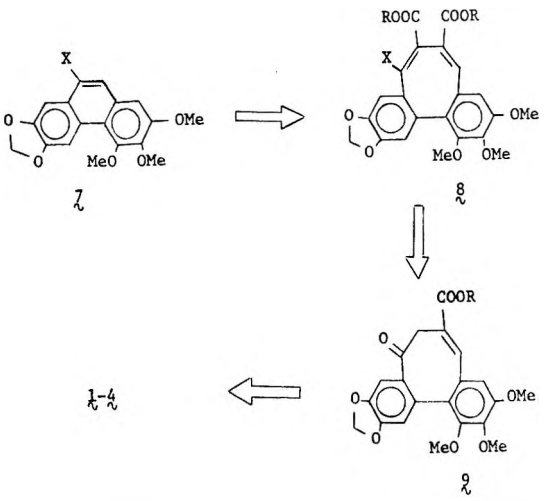
1 R_1 = OAc, R_2 = H
2 R_1 = OOC–, R_2 = H
3 R_1 = OH, R_2 = H
4 R_1, R_2 = O

derivatives of the β-alcohol steganol **3**), there has been considerable interest in the synthesis of this class of dibenzo[*a*,*c*]cyclooctadiene.[3,4] In light of recent publications on the total syntheses of steganone **4** and its companion lignans **1**–**3**,[4] we wish to report our independent synthetic efforts similar to those of Raphael[4a] in this area.

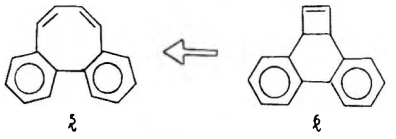
The general approach which was conceived for the synthesis of the lignans **1**–**4** is outlined in Scheme I. The critical feature of our plan was to find a method for the formation of the dibenzocyclooctadiene skeletal system of these lignans. The precedent for our synthetic approach was the synthesis of dibenzocyclooctatetraene **5** by a 2 + 2 cycloaddition utilizing the 9,10 bond of phenanthrene, followed by electrocyclic ring opening of an intermediate cyclobutene **6**.[5] We envisioned the 2 + 2 cycloaddition of an acetylenedicarboxylic acid ester or masked acetylene equivalent to an appropriately substituted phenanthrene **7**, followed by concomitant thermal ring opening of an initially formed cyclobutene, would lead to a dienamine or dienol ether **8**. Hydrolysis might afford **9**, a template for elaboration of the lactone ring of steganone **4**. The ketone steganone **4** has been converted by Kupchan[2] to steganol **3**, the parent alcohol from which steganacin **1** and steganangin **2** are derivable.[2,4a,b]

Oxidative photochemical ring closure of stilbene α-carboxylic acids is a straightforward entry to phenanthrene-9-carboxylic acids,[6] and 3,4-methylenedioxy-3′,4′,5′-trime-

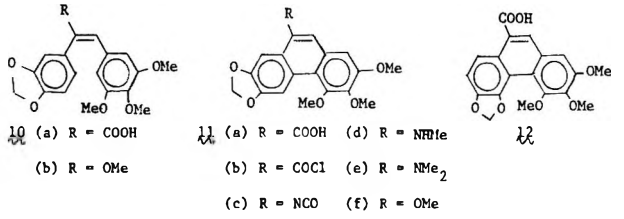
Scheme I



thoxy-α-carboxystilbene[7] (**10a**) upon irradiation for 20 h in benzene with iodine oxidant afforded in 81% yield the 9-car-



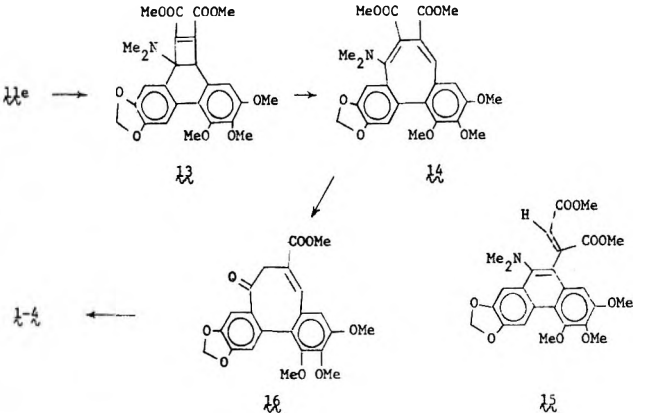
boxyphenanthrene **11a**. The structure of **11a** was distinguished from its isomer **12** by the observation of four 1-proton singlets in the aromatic region of the NMR spectrum; **12** would show ortho-proton coupling (J = 6–10 Hz).[8]



Although acids can generally be converted to amines with one less carbon atom by a variety of methods,[9] a major difficulty when we began this research was the reported[9b,c] low yield in the conversion of phenanthrene-9-carboxylic acids into the corresponding 9-phenanthrylamines by a variety of Curtius and related rearrangements. This problem was overcome[10] by refluxing the acid chloride of 9-carboxyphenanthrene **11b** with trimethylsilyl azide in refluxing benzene[11] to afford 9-phenanthryl isocyanate **11c**. Reduction of **11c** with lithium aluminum hydride in freshly distilled tetrahydrofuran afforded the N-methylamine **11d**, which was methylated with trimethyl phosphate[12] to afford dimethylamine **11e** in 80% overall yield from acid **11a**.[13]

In an attempt to prepare the methoxyphenanthrene **11f**, the α-methoxystilbene **10b**, prepared by methylation of the corresponding deoxybenzoin with methyl fluorosulfonate in hexamethylphosphoramide,[14] was irradiated under oxidative conditions. However, only the deoxybenzoin could be recovered.[15]

Although maleic anhydride, diethyl maleate, and diethyl fumarate can be photochemically added to phenanthrene,[5,16] attempted photochemical cycloadditions of diethyl fumarate, bromomaleic anhydride, or dimethyl acetylenedicarboxylate to 9-dimethylaminophenanthrene **11e** were unsuccessful.[17] However, reports of two-carbon ring expansion of enamines[18] suggested a thermal cycloaddition of dimethyl acetylenedicarboxylate with **11e** might be successful if the 9,10 bond of the phenanthrene **11e** were to have sufficient enamine character. The desired cycloaddition to afford **14** was effected in



50% yield in refluxing dioxane solvent. The NMR spectrum of **14** showed four 1-proton singlets in the downfield olefinic–aromatic region, ruling out the cyclobutene structure **13**. Structure **15** was ruled out by hydrolysis of **14** with refluxing methanolic hydrochloric acid to afford in 80% yield the unsaturated keto ester **16**, which has previously been utilized by Raphael[19] to synthesize steganone **4** and its companion lignans **1**–**3**.[20]

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were done by Atlantic Microlab, Inc., Atlanta, Ga., or Micro-Analysis, Inc., Wilmington, Del. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A60-A or XL-100 Model. Chemical shifts are reported in δ units using tetramethylsilane as an internal standard.

Tetrahydrofuran was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. In all workup procedures the drying process involved treatment with anhydrous magnesium or sodium sulfates and filtering prior to concentration in vacuo. Thin-layer chromatography was performed using precoated Woelm silica gel GF plates. Dry column chromatography was done using Woelm silica gel for the dry column from Analtec, Inc.

2,3,4-Trimethoxy-6,7-methylenedioxy-9-carboxyphenanthrene (11a). 3′,4′,5′-Trimethoxy-3,4-methylenedioxy-α-carboxystilbene (**10a**) (3.4 g, 9.6 mmol), synthesized according to a known procedure,[7] in benzene (500 mL) and iodine (120 mg) was irradiated for 20 h as described by Mallory.[6a] Workup afforded **11a** (2.75 g, 81%) as yellow needles: mp 146–147 °C; NMR (Me_2SO-d_6) δ 4.17 (9 H, s), 6.48 (2 H, s), 7.70 (1 H, s), 8.61 (2 H, s), 9.19 (1 H, s); UV (EtOH) λ_{max} 258 (ε 85 000) and 284 nm (ε 32 000).

Anal. Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53. Found C, 63.97; H, 4.56.

***N*-Methyl-2,3,4-trimethoxy-6,7-methylenedioxy-9-aminophenanthrene (11d).** Phenanthrene-9-carboxylic acid **11a** (2.0 g, 5.6 mmol) was converted to its sodium salt with sodium methoxide in methanol. After the removal of solvent, the salt was refluxed with oxalyl chloride (10 mL) in benzene (50 mL) for 2 h. Distillation of the benzene and oxalyl chloride and removal of the residual solvent in vacuo left a light-yellow solid **11b**. The acid chloride **11b** in benzene (30 mL) and trimethylsilyl azide (4 mL, TMSA, Aldrich) were stirred for 1 h at room temperature and then heated at reflux for 24 h. Removal of the benzene and excess TMSA in vacuo afforded a solid isocyanate **11c**, which was dissolved in dry tetrahydrofuran (20 mL) and added dropwise to lithium aluminum hydride (500 mg, 13.5 mmol) in tetrahydrofuran (100 mL) under nitrogen. After stirring at room temperature for 1 h, the mixture was refluxed for 2 h. After destruction of the excess $LiAlH_4$, filtration, and washing of the precipitated salts with tetrahydrofuran, the combined organic layers were dried over sodium sulfate. Removal of solvent in vacuo afforded a light-tan solid **11d**, 1.64 g (84%), mp 195–197 °C, which could be further purified by dry column chromatography (Woelm silica gel, activity III): mp 198 °C (CH_3OH/$CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (3 H, s), 4.12 (9 H, m), 6.42 (2 H, s), 6.88 (1 H, s), 7.32 (1 H, s), 8.00 (1 H, s), 9.12 (1 H, s); UV λ_{max} (ethanol) 260 (ε 60 000) and 290 nm (ε 37 000).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.87; H, 5.61; N, 4.10. Found: C, 66.95; H, 5.64; N, 4.12.

Addition of methanol to isocyanate **11c** and heating for 24 h afforded upon removal of solvent and chromatography on silica gel the

urethane, mp 215–216 °C (methanol). The urethane could be synthesized directly from the acid **11a** in 28% yield using diphenylphosphoryl azide in methanol with triethylamine catalysis.[10,21] However, there was almost no hydrolysis of the urethane of **11c** after a 48-h reflux in 1:1 ethylene glycol/50% aqueous potassium hydroxide. Lithium aluminum hydride reduction of the urethane in refluxing tetrahydrofuran afforded only a 5% yield of methylamine **11d** after 48 h.[10]

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.53; H, 4.85; N, 3.75.

***N,N*-Dimethyl-2,3,4-trimethoxy-6,7-methylenedioxy-9-aminophenanthrene (11e).** A mixture of *N*-methyl-9-aminophenanthrene **11d** (1.0 g, 2.9 mmol) and trimethyl phosphate[12] (5 mL) was refluxed under nitrogen for 2 h. Excess trimethyl phosphate was distilled in vacuo, ethanol (5 mL) was added, and aqueous sodium hydroxide (10%) was added until the solution was alkaline. The solution was refluxed for 1.5 h, and the resulting solid was filtered, washed with cold aqueous ethanol, and recrystallized from methanol to give **11e**: 0.9 g (87%); mp 157–158 °C; NMR (Me_2SO-d_6) δ 2.89 (6 H, s), 3.82–4.00 (9 H, m), 6.32 (2 H, s), 7.5 (2 H, d), 7.89 (1 H, s), 9.16 (1 H, s); UV λ_{max} (ethanol) 258 (ε 74 000) and 287 nm (ε 44 000).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.67; H, 5.95; N, 3.91.

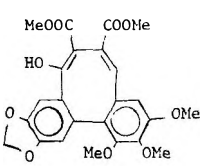
Heating of the dimethylenamine **11e** with pyrrolidine neat, in methanol, or in dioxane with *p*-toluenesulfonic acid catalysis afforded unchanged **11e** and did not result in enamine exchange.

Dimethyl 1,2,3-Trimethoxy-10,11-methylenedioxy-8-*N,N*-dimethylaminodibenzo[*a,c*]cyclooctatetraene-6,7-dicarboxylate (14). Dimethylaminophenanthrene **11e** (178 mg, 0.5 mmol) and dimethyl acetylenedicarboxylate (DMADC) (720 mg, 5 mmol) were refluxed in dioxane for 5 days. Solvent and excess DMADC were removed in vacuo to afford a dark-brown gum (0.71 g) which was chromatographed (Analtech preparative layer silica gel, 50:50 ethyl acetate/hexane and 9:1 benzene/ethyl acetate as eluents) to afford dienamine diester **14**: 124 mg (50%); mp 203–205 °C; NMR ($CDCl_3$) δ 7.26 (1 H), 6.70 (1 H), 6.60 (1 H), 6.58 (1 H), 5.98 (2 H), 3.6–3.9 (5 s, OCH_3), 2.78 (s, 6 H); IR ($CHCl_3$) 5.85 and 6.0 μm; UV (ethanol) λ_{max} 344 (log ε 4.88), 302 (log ε 5.16), 248 (shoulder) nm (log ε 5.32).

Alternately, **11e** (600 mg, 1.5 mmol) and DMADC (0.4 mL) were heated at 125 °C in dimethyl sulfoxide (25 mL) for 24 h under nitrogen. Additional DMADC (0.2 mL) was added every 12 h for 5 days until **11e** had disappeared by TLC. Workup as above afforded **14**, 252 mg (35%).

Anal. Calcd for $C_{26}H_{27}NO_9$: C, 62.77; H, 5.43; N, 2.81. Found: C, 62.65; H, 5.47; N, 2.81.

Methyl 7,8-Dihydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[*a,c*]cyclooctatetraene-6-carboxylate (16). Dibenzocyclooctatetraeneenamine diester **15** (90 mg, 0.18 mmol) was hydrolyzed by refluxing with 5:1 methanol/6 N hydrochloric acid (v/v) (6 mL) for 8 h. Water (5 mL) was added to the cooled solution, which was extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was removed to afford an oil (76 mg) which upon chromatography on silica gel (9:1 benzene/ethyl acetate) afforded keto monoester **16**: 59 mg (80%); mp 145–147 °C.[19] Also obtained was 8-hydroxydibenzocyclooctatetraene 6,7-diester **19**: 17 mg (20%); mp 177–179 °C; NMR

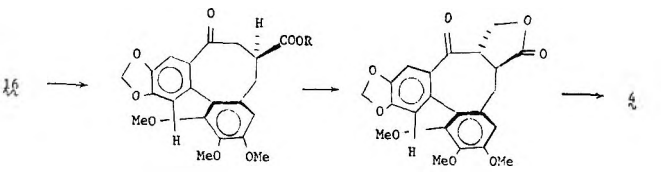


19

($CDCl_3$) δ 8.74 (1 H), 7.70 (1 H), 6.96 (1 H), 6.60 (1 H), 6.54 (1 H), 6.20 (2 H), 3.98 (3 H), 3.92 (3 H), 3.80 (6 H), 3.54 (3 H). The diester **19** and the monoester **16** need not be separated, since hydrogenation followed by basic hydrolysis of the mixture affords keto acid **17b** (80%).[20]

Methyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[*a,c*]cyclooctatetraene-6-carboxylate (17a). Dibenzocyclooctatrienone monoester **16** (95 mg, 0.45 mmol) was catalytically hydrogenated at 35 psi in methyl acetate (50 mL) with W-2 Raney nickel for 24 h at 25 °C. Filtration and removal of solvent afforded quantitatively keto ester **17a**, mp 132–132.5 °C (ether/hexane). With some batches of Raney nickel carbonyl reduction occurred to a small extent; the crude reaction mixture was then oxidized with Jones reagent to the keto ester **17a**.

It has been shown[4a,b] that upon melting or after standing in solution **17a** epimerizes partially to a less polar isomeric ester (*RR/SS*), which



upon hydrolysis and hydroxymethylation leads directly to steganone **4**. Keto ester **17a** upon similar treatment affords isosteganone **18**, which can be isomerized quantitatively to steganone **4**.[4a,b]

Acknowledgment. We gratefully acknowledge Dr. R. M. Carlson for helpful suggestions, Drs. A. S. Kende and L. S. Liebeskind for spectra and samples of **4**, **17a**, and **17b**, Dr. R. A. Raphael for spectra and a sample of **16**, P. Conroy and D. Shaw for technical assistance, and financial support from the National Institutes of Health (Grant CA-15759) and the National Science Foundation (Grant CHE-05757).

Registry No.—**4**, 58800-45-6; **10a**, 60848-05-7; **11a**, 60848-06-8; **11a** Na salt, 67316-77-2; **11b**, 67316-78-3; **11c**, 60848-09-1; **11c** urethane derivative, 60848-07-9; **11d**, 60848-08-0; **11e**, 67316-79-4; **14**, 67316-80-7; **15**, 67316-81-8; **16**, 60546-67-0; **17a**, 65310-10-3; **17b**, 65310-09-0; **18**, 65310-12-5; **19**, 67316-82-9; dimethyl acetylenedicarboxylate, 762-42-5.

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(19) Compound **16** was identical by TLC and NMR spectral comparison with a sample provided by Dr. R. A. Raphael. The position of the double bond has been assigned by Raphael.[4a]

(20) Catalytic hydrogenation of **16** in methyl acetate with W-2 Raney nickel (35 psi, 24 h) produced the keto ester **17a**, identical by TLC and NMR spectral comparison with an authentic sample provided by Drs. A. S. Kende and L. S. Liebeskind.[4b] Raphael[4a] reports hydrogenation of **16** occasionally results in the formation of a hydroxy compound, which upon oxidation with Jones reagent affords the saturated keto ester **17a**. We have also noted carbonyl recuction with some batches of Raney nickel. Keto ester **17a** has previously been converted by hydrolysis to **17b**, which reacts with formaldehyde in base to form isosteganone **18**. Thermally, **18** is converted quantitatively to steganone **4**.[4a,b]

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Synthesis of *N,N*-Dialkylaminosulfenylcarbamate Insecticides via Carbamoyl Fluorides

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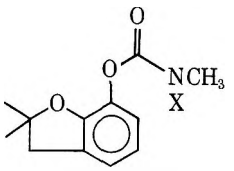
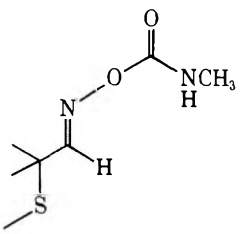
A facile and general process for the preparation of *N*-sulfenylated carbamates from carbamoyl fluorides and alcohols under phase-transfer conditions is described. Use of this method to prepare a series of 12 analogues of the carbamate insecticides carbofuran, methomyl, and carbaryl is discussed. The preparation and properties of the intermediate carbamoyl fluorides are also reported.

One of the major deficiencies of the widely used carbamate class of insecticides is their generally high mammalian toxicity. For example, carbofuran (**1a**) has an oral LD_{50} in rats of 11 mg/kg while for aldicarb (**2**) the value is only 1 mg/kg.[1]



1a, X = H
b, X = SR



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With the goal of maintaining the insecticidal activity but decreasing the mammalian toxicity, a large number of analogues of carbamates have been synthesized. One group of analogues, which are considerably less toxic to mammals but which are cleaved by insects to the parent carbamate, is composed of *N*-sulfur compounds such as **1b**. Of particular interest to us were **1b** type compounds where R = $N(alkyl)_2$, which were originally prepared by Fukuto and Black.[2] Their preparation of these materials involved condensation of carbofuran with the appropriate sulfenyl chloride. Because of certain patent restrictions, we desired a general synthesis of dialkylaminosulfenylcarbamate analogues which did not utilize the parent carbamate either as a starting material or as an intermediate. Toward this goal we examine the approach outlined in Schemes I and II, which involves as a key intermediate an *N*-dialkylaminosulfenyl-*N*-alkylcarbamoyl fluoride. A related route, which had been previously reported for the preparation of SAr and SCX_3 (S = halogen or hydrogen) carbamate derivatives,[3] was found to work very poorly in our hands. Utilizing the process described herein, a series of dialkylaminosulfenyl derivatives of commercial carbamates was prepared in high yield and purity.[4,5]

Although *N*-methylcarbamoyl fluoride (**3**, see Scheme I) has been utilized in a number of patents,[3] a detailed report of its synthesis could not be found. There are several possible synthetic approaches to the material; however, only the reaction of methyl isocyanate (MIC) and anhydrous hydrogen fluoride (HF) was examined. All work with HF was carried out in polyethylene bottles equipped with polyethylene tubing and stopcocks.

Scheme I

$$CH_3NCO + HF \rightarrow \underset{\mathbf{3}}{CH_3NHCOF}$$

$$\underset{\mathbf{4}}{R^1R^2NH} + S_2Cl_2 \rightarrow \underset{\mathbf{5}}{(R^1R^2NS)_2}$$

$$\underset{\mathbf{5}}{(R^1R^2NS)_2} + SO_2Cl_2 \rightarrow \underset{\mathbf{6}}{R^1R^2NSCl}$$

$$\underset{\mathbf{3}}{CH_3NHCOF} + \underset{\mathbf{6}}{R^1R^2NSCl} \rightarrow \underset{\mathbf{7}}{R^1R^2NSN(CH_3)COF}$$

	R^1	R^2
4a–7a	*n*-Bu	*n*-Bu
4b–7b	morpholino	
4c–7c	*n*-Pr	*n*-Pr
4d–7d	Me	$CH_2C_6H_5$
4e–7e	Et	$CH_2C_6H_5$
4f–7f	piperidino	
4g–7g	Et	Et

Treatment of a solution of MIC in methylene chloride with 2–5 equiv of gaseous HF (bp 19 °C) at 0 °C over 1 h followed by removal of the solvent and excess HF under vacuum at 30

Scheme II

$$\underset{\mathbf{7}}{R^1R^2NSN(CH_3)COF} + \underset{\mathbf{8}}{R^3OH} \rightarrow \underset{\mathbf{9}}{R^1R^2NSN(CH_3)CO_2R^3}$$

	R^1	R^2	R^3
8h			2,2-dimethylbenzofuran-7-yl
i			$CH_3S(CH_3)C{=}N$
j			napth-1-yl
k			CH_3
9l	*n*-Bu	*n*-Bu	2,2-dimethylbenzofuran-7-yl
m	morphilino		2,2-dimethylbenzofuran-7-yl
n	Et	$CH_2C_6H_5$	2,2-dimethylbenzofuran-7-yl
o	*n*-Bu	*n*-Bu	$CH_3S(CH_3)C{=}N$
p	*n*-Pr	*n*-Pr	$CH_3S(CH_3)C{=}N$
q	CH_3	$CH_2C_6H_5$	$CH_3S(CH_3)C{=}N$
r	Et	Et	$CH_3S(CH_3)C{=}N$
s	*n*-Bu	*n*-Bu	napth-1-yl
t	*n*-Pr	*n*-Pr	napth-1-yl
u	Et	$CH_2C_6H_5$	napth-1-yl
v	piperidino		napth-1-yl
w	Et	Et	napth-1-yl
x	*n*-Bu	*n*-Bu	CH_3

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Table I. Preparation of *N*-Dialkylaminosulfenyl-*N*-methylcarbamoyl Fluorides from *N*-methylcarbamoyl Fluoride

fluoride	registry no.	isolated[a] yield, %	Bp (pressure, mm) or mp, °C	elemental anal.[b] calcd (found) C	H	N	NMR (CCl_3D), δ
7a	62382-48-3	61	84–85 (0.2–0.3)	50.82 (51.15)	8.96 (8.84)	11.85 (11.99)	0.80–2.00 (m, 14), 3.15 (bt, 4, NCH_2), 3.30 (s, 3, $CONCH_3$)
7b	62382-41-6	38	49–50	37.12 (36.86)	5.79 (5.62)	14.43 (14.34)	3.10–3.40 (m, 4,), 3.40 (s, 3, $CONCH_3$), 3.60–3.80 (m, 4)
7c	67271-00-5	53	59–60 (0.2–0.3)	46.13 (46.60)	8.23 (8.10)	13.45 (13.92)	0.95 (t, 6, CH_2CH_3), 1.20–2.00 (m, 4, CH_2CH_3), 3.10 (bt, 4, NCH_2), 3.30 (s, 3, $CONCH_3$)
7d	67271-01-6	47	99–100 (0.2–0.3)	53.10 (52.49)	5.08 (5.62)	12.42 (12.09)	2.85 (s, 3, $SN[CH_3]CH_2$), 3.30 (s, 3 $CONCH_3$), 4.30 (bs, 2, NCH_2), 7.25 (s, 5, $CH_2C_6H_5$)
7e	67271-02-7	60	104–105 (0.2–0.3)	54.52 (55.19)	6.24 (6.89)	11.56 (12.10)	1.20 (t, 3, CH_2CH_3), 3.10 (q, 2, CH_2CH_3), 3.35 (s, 3, $CONCH_3$), 4.40 (bs, 2, NCH_2), 7.25 (s, 5, $CH_2C_6H_5$)
7f	62382-43-8	59	65–66 (0.2–0.3)	43.73 (44.24)	6.82 (6.78)	14.57 (14.84)	1.35–1.80 (m, 6), 3.25 (bt, 4 NCH_2), 3.35 (s, 3 $CONCH_3$)
7g	62382-46-1	45	43–44 (0.2–0.3)	39.98 (40.48)	7.27 (7.30)	15.54 (15.37)	1.20 (t, 6, CH_2CH_3), 3.15 (q, 4, CH_2CH_3), 3.30 (s, 3, $CONCH_3$)

[a] Either distilled or recrystallized from hexane. [b] Many of these materials which contain N–S–N bonding are unstable when analytically pure. As such, high accuracy combustion analyses were difficult to obtain.

°C gave a high yield of a crude liquid product. Attempts to transfer this product to glassware for analysis, storage, or distillation were unsuccessful, due to reaction of the material with any glass equipment. Substitution of pentane for the methylene chloride solvent resulted in a two-phase system after addition of the HF since both HF and the fluoride **3** are only slightly soluble in hydrocarbon solvents. In this case, removal of the solvent and excess HF as described above gave a crude liquid which could be handled and distilled in glassware. Distilled fluoride **3** (bp 30–35 °C at 0.5—1.0 mm), which was obtained in a 93% yield, could be stored in glassware at 0 °C for several months with no appreciable decomposition. On a routine basis, however, **3** was used as a residual product and handled only in polyethylene.

The dialkylamino disulfides (**5a–g**, see Scheme I) which were used in this work were prepared from the corresponding amines (**4a–g**) and sulfur monochloride. Initially they were obtained by reaction in carbon tetrachloride of 4 equiv of the amine with 1 equiv of sulfur monochloride; however, due to the problem of amine recover, better conditions were sought. It was found that addition of sulfur monochloride to a vigorously stirred two-phase mixture of 2 equiv of amine, hexane, sodium hydroxide, and water at 0 °C gave after 1 h the desired disulfide in high yield and good purity. In general the disulfides prepared in this manner were used without further purification. In the case of **5a**, samples of the corresponding monosulfide (**10**) and trisulfide (**11**) were prepared and shown by NMR and LC to be minor contaminants in the disulfide. Usually a small amount of solid, which was shown by LC to be elemental sulfur, precipitated out of the liquid disulfides on storage below room temperature.

Cleavage of the disulfides **5a–g** to the corresponding sulfenyl chlorides **6a–g** was examined both with chlorine gas in carbon tetrachloride solution and with sulfuryl chloride neat. Although the crude yields were good from both approaches, the latter was found preferable since it required the minimum amount of manipulation of the sulfenyl chlorides which generally, over several hours, darkened in color and formed amine hydrochloride salt precipitates. Some of the sulfenyl chloride **6a** was successfully flash distilled (bp 65–70 °C at 0.1–0.2 mm) although in low yield. Attempted batch distillation of similar material was unsuccessful. Routinely the appropriate disulfide was treated at 0–10 °C with 1 to 1.1 equiv of sulfuryl chloride for 1 h, followed by removal of any excess sulfuryl chloride and the sulfur dioxide by-product under vacuum. The thus obtained products were used immediately.

The reaction of di-*n*-butylaminosulfenyl chloride, **6a**, with *N*-methylcarbamoyl fluoride, **3**, to give the N,N-disubstituted carbamoyl fluoride **7a** was initially examined under literature conditions[3] for a similar transformation which involved reaction of equimolar quantities of the starting materials in a nonpolar organic solvent in the presence of a tertiary amine base for several hours. It was shown, however, that for the dialkylamino system these conditions resulted in both a very low yield and low purity of the desired product **7a**. As a result, other conditions were examined utilizing an n-$C_{13}H_{28}$ internal standard coupled with GLC analysis on a 10% OV17 Chromosorb W column. From these experiments it was found that use of a polar solvent such as pyridine at room temperature with 1.5 equiv of 1,4-diazabicyclo[2.2.2]octane base for several hours gave an 80–85% yield of crude **7a** (carbonyl IR at 1780 cm^{-1}) which was stable in glassware and could be purified by distillation to give a 75–80% yield of **7a** of >95% purity. The crude material was also purified by column chromatography; however, the recovery was only 25–30% indicating some reaction of **7a** with the silica packing. Although differential thermal analysis of **7a** indicated an exotherm of ~200 cal/g at 200 °C, no problems were encountered in its distillation. In methanol–triethylamine solution fluoride **7a** was converted to the corresponding methyl ester (**9x**) (carbonyl IR at 1740 cm^{-1}) which was also prepared from the sulfenyl chloride **6a** and the known methyl *N*-methylcarbamate.

Using conditions similar to those for the preparation of **7a**, the fluorides **7b–g** (see Table I) were prepared. All were liquids which were purified by distillation with the exception of the morpholino **7b** which was a solid (recrystallized from hexane) and the methylbenzylamino **7d** which slowly solidified after distillation. All of these fluorides could be analyzed by GLC on 10% OV17 on Chromosorb W except the ethylbenzyl **7e** which underwent partial decomposition.

The reaction of carbamoyl fluoride **7a** with the alcohol **8h** to give the carbamate **91** was examined under various conditions. The reactions were followed by the loss of the fluoride peak on GLC against an n-$C_{13}H_{28}$ internal standard. Initially tried were conditions involving the reaction of equimolar amounts of the carbamoyl fluoride and alcohol in the presence of a tertiary amine base in a number of organic solvents at, or slightly above, room temperature. Thermal sensitivity of the final product prohibited utilizing higher reaction temperatures. However, it was found that for the carbamoyl fluoride **7a** and alcohol **8h**, these conditions resulted in reaction times of several days and product in low yield and purity (see Table II).

As a result of the apparent stability of the carbamoyl fluo-

Table II. Equimolar Reactions of *N*-(Di-*n*-butylaminosulfenyl)-*N*-methylcarbamoyl Fluoride (7a) with 7-Hydroxy-2,3-dihydro-2,2-dimethylbenzofuran (8h)

run	solvent	catalyst[a]	base	reaction time, (h)	reaction temp, °C	product (9l) % purity[b]	product (9l) % yield[c]
1	toluene		TEA[d]	20	ambient	26	11
				2	45		
2	acetonitrile		TEA	20	ambient	36	14
				2	45	36	14
3	toluene	tetrabutylammonium hydrogen sulfate	NaOH	2	ambient	86	73 (69[e])
4	methylene chloride	benzyltriethyl ammonium chloride	NaOH	6.5	ambient	66	80

[a] 10 mol %. [b] By LC on a C-18 reverse phase column against a purified standard. [c] Crude weight X LC determined purity. [d] TEA = triethylamine. [e] Isolated by silica gel column chromatography.

Table III. Reactions of *N*-Dialkylaminosulfenyl-*N*-methylcarbamoyl Fluorides with Alcohols

carbamate	registry no.	alcohol	isolated[a] yield, %	Mp, °C (or n^{20}_D)	elemental anal.[b] calcd (found) C	H	N	NMR (CCl_3D), δ
9l	55285-14-8	**8h**[c]	69	(1.5116)	63.13 (63.16)	8.48 (8.49)	7.36 (7.67)	0.80–2.00 (m, 14), 1.50 (s, 6, $C[CH_3]_2$), 3.00 (s, 2, ring CH_2), 3.20 (t, 4, NCH_2), 3.40 (s, 3, $CONCH_3$), 6.60–7.10 (m, 3, aromatic)
9m	55285-05-7	**8h**	75	80–81	56.79 (56.69)	6.55 (6.36)	8.28 (8.13)	1.45 (s, 6, $C[CH_3]_2$), 3.05 (s, 2, ring CH_2), 3.20–3.45 (m, 4), 3.45 (s, 3, $CONCH_3$), 3.60–3.80 (m, 4), 6.70–7.30 (m, 3, aromatic)
9n	55285-18-2	**8h**	65	(1.5606)	65.27 (65.13)	6.78 (6.78)	7.25 (6.96)	1.20 (t, 3, CH_2CH_3), 1.45 (s, 6, $C[CH_3]_2$), 3.05 (s, 2, ring CH_2), 3.20 (q, 2, CH_2CH_3), 3.45 (s, 3, $CONCH_3$), 4.60 (bs, 2, $CH_2C_6H_5$), 6.80–7.40 (m, 3, benzofuranyl aromatic), 7.35 (s, 5, C_6H_5)
9o	62382-35-8	**8i**[d]	69	(1.5080)	48.57 (49.07)	8.47 (8.44)	13.07 (13.63)	0.85–1.90 (m, 14), 2.25 (s, 3), 2.30 (s, 3), 3.20 (bt, 4, NCH_2), 3.30 (s, 3, $CONCH_3$)
9p	67271-03-8	**8i**	45	(1.5160)	45.04 (44.99)	7.90 (7.66)	14.33 (14.03)	0.90 (t, 6, CH_2CH_3), 1.40–2.00 (m, 4, CH_2CH_3) 2.25 (s, 3), 2.30 (s, 3), 3.15 (bs, 4, NCH_2), 3.35 (s, 3, $CONCH_3$)
9q	67271-04-9	**8i**	60	87–88	49.82 (49.69)	6.11 (6.08)	13.41 (13.18)	2.30 (s, 3), 2.35 (s, 3), 2.90 (s, 3, $SN[CH_3]CH_2$), 3.45 (s, 3, $CONCH_3$), 4.40 (s, 2, NCH_2), 7.35 (s, 5, C_6H_5)
9r	62382-32-5	**8i**	70	(1.5284)	40.73 (40.62)	7.22 (7.06)	15.83 (15.59)	1.20 (t, 6, CH_2CH_3), 2.30 (s, 3), 2.35 (s, 3), 3.25 (q, 4, CH_2CH_3), 3.40 (s, 3, $CONCH_3$)
9s	67316-53-4	**8j**[e]	67	(1.5486)	66.64 (66.31)	7.83 (7.74)	7.77 (7.70)	0.70–1.90 (m, 14), 3.25 (bt, 4, NCH_2), 3.50 (s, 3, $CONCH_3$), 7.30–8.10 (m, 7, napthyl)
9t	67271-05-0	**8j**	54	(1.5744)	65.04 (64.69)	7.28 (7.09)	8.43 (8.16)	0.85 (t, 6, CH_2CH_3), 1.40–2.05 (m, 4, CH_2CH_3), 3.25 (bt, 4, NCH_2), 3.50 (s, 3, $CONCH_3$), 7.20–8.20 (m, 7, napthyl)
9u	67271-06-1	**8j**	63	47–49	68.83 (69.20)	6.05 (6.33)	7.65 (8.15)	1.05 (t, 3, CH_2CH_3), 3.20 (q, 2, CH_2CH_3), 3.50 (s, 3, $CONCH_3$), 4.55 (bs, 2, $CH_2C_6H_5$), 7.20–8.10 (m, 7, napthyl), 7.25 (s, 5, C_6H_5)
9v	67271-07-2	**8j**	38	77–78	64.54 (64.89)	6.37 (6.30)	8.86 (8.93)	1.30–1.70 (m, 6), 3.20–3.50 (m, 4), 3.50 (s, 3, $CONCH_3$), 7.20–8.10 (m, 7, napthyl)
9w	67271-08-3	**8j**	45	(1.5801)	63.14 (63.39)	6.62 (6.80)	9.21 (8.95)	1.20 (t, 6, CH_2CH_3), 3.25 (q, 4, CH_2CH_3), 3.45 (s, 3, $CONCH_3$), 7.10–8.10 (m, 7, napthyl)

[a] Chromatographed on silica gel. [b] Many of these materials which contain N–S–N bonding are unstable when analytically pure. As such, high accuracy combustion analyses were difficult to obtain. [c] Registry no. 1563-38-8. [d] Registry no. 13749-94-5. [e] Registry no. 90-15-3.

ride **7a** to attack at the acyl carbon, more severe reaction conditions were sought. It was found that under phase transfer conditions[6] involving an organic solvent–water mixture utilizing a quarternary ammonium salt catalyst and sodium hydroxide base, the desired transformation occurred rapidly and gave product of high purity in good yield. Both tetrabutylammonium hydrogen sulfate and benzyltriethylammonium chloride were examined as catalyst in several solvents. For the preparation of **9l**, a 10 mol % quanitity of the tetrabutylammonium hydrogen sulfate in toluene solvent was the best combination. The use of an excess of base increased the reaction rate considerably. The best conditions (see Table II) gave in 2 h an 85% yield of crude **9l** which was 86% pure as determined by quantitative LC analysis on a μ-particle C-18 reverse phase column using acetonitrile–water eluant. A 69% yield of high purity **9l** was isolated by column chromatography on silica gel.

The reactions of **7a** with the alcohols **8i** and **8j**, to give respectively **9o** and **9s**, were also examined under phase-transfer conditions with several different catalysts and organic solvents. In a manner similar to **8h**, the aromatic alcohol **8j** was found to react best with **7a** using toluene solvent and a 10 mol % quantity of tetrabutylammonium hydrogen sulfate catalyst for 2–3 h. In contrast to **8h** and **8j**, the nonaromatic alcohol **8i** was found to react best with **7a** in methylene chloride using a 10 mol % quantity of benzyltriethylammonium chloride catalyst. This latter reaction was significantly slower, requiring 22 h for completion.

Using the specific conditions worked out for each of the three alcohols, **8h–j**, described above, the 12 carbamate de-

rivatives in Table III were prepared. In all cases the NMR spectra were consistent with the desired product containing small amounts of impurities. Reactions involving alcohol **8j** had a strong propensity to turn black upon exposure to air, in contrast to the reactions of the other alcohols.

The carbamate products were all found to be active insecticides with lower mammalian toxicity than the corresponding parent compound. For example, the parent compound carbofuran, **1a**, has an oral LD_{50} in rats of 11 mg/kg and causes death at 0.1 mg/eye in a rabbit eye irritation test while the di-*n*-butylaminosulfenyl analogue of carbofuran, **9l**, in the same tests, had values of 105 mg/kg for the rat LD_{50} and no reaction in the rabbit eye test.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 735B spectrometer. NMR spectra were recorded either on a Varian T-60 or XL-100 instrument using $CDCl_3$ solvent and tetramethyl silane reference. Mass spectra (70 eV) were recorded on a DuPont 21-490B instrument. Microanalyses were determined by the Analytical Department of FMC Corp., Princeton, N.J. LC work was performed on a Waters Associates instrument equipped with a 254 nm fixed wavelength UV photometer detector and a 30 cm × 4 mm i.d. SS u-Bondapak C-18 reverse phase partition column. GLC work was carried out on a Hewlett-Packard 5840A instrument equipped with a thermal conductivity detector and a 6 ft. × 1/8 in. i.d. stainless steel column packed with 10% OV 17 on Chromosorb W. In all cases hexane and pentane were mixtures of isomers.

***N*-Methylcarbamoyl Fluoride (3).** Through the cap of a 2 oz. polyethylene bottle were run two 1/4 in. i.d. polyethylene tubes, one of which extended to the bottom of the vessel (inlet tube) and one which went only through the cap (vent tube). After sealing the two tubes in place with epoxy, polyethylene stopcocks were attached to the ends of both tubes. A length of polyethylene tubing was run from the stopcock on the "inlet tube" to a cylinder of anhydrous hydrogen fluoride (HF), while another piece was run from the stopcock on the "vent tube" to an aqueous sodium hydroxide trap. To the reaction vessel was charged methyl isocyanate (10.0 g, 0.175 mol) and pentane (30 mL). To the resulting solution stirred and cooled to 0 °C was added a slow stream of HF (2–5 equiv) over 1 h. The HF (bp 19 °C) liquidified in the reactor during the addition and at the end of the addition two phases were present in the reactor. The HF flow was replaced by a nitrogen flow and the solution was warmed to 30 °C. After the pentane (upper layer) and any excess HF had distilled into the trap, the reaction mixture was transferred to a 1 oz. polyethylene bottle and placed under a vacuum of 2–5 mm for 30 min to give 13.40 g (99% yield by weight of a colorless liquid). This was transferred to glassware and distilled to give 12.51 g (93%) of colorless **3:** bp 30–35 °C (0.5–1.0 mm); NMR (CCl_3D) δ 2.85 (d, 3, NCH_3), 6.00 (broad s, 1, NH); mass spectrum (70 eV) *m/e* 77 (M+).

The material, if totally free of HF, could be stored at least several months in glassware; however, it was best stored in polyethylene containers. For most of our work the crude material was placed under high vacuum but not distilled.

Anal. Calcd for C_2H_4NOF: C, 31.17; H, 5.23; N, 18.18; F, 24.65. Found: C, 31.24; H, 5.27; N, 18.17; F, 24.41.

Bis(di-*n*-butylamino) Disulfide (5a). To a rapidly stirred and cooled to 0 °C two-phase system composed of water (1800 mL), hexane (750 mL), di-*n*-butylamine (516.0 g, 4.00 mol, 1.00 equiv), and sodium hydroxide (211.6 g, 5.29 mol, 1.32 equiv) was added over 10 min a solution of sulfur monochloride (310.0 g, 2.30 mol, 1.14 equiv) in hexane (500 mL) which was protected from moisture until the addition. The cooling bath was removed and the mixture stirred an additional 45 min. The water layer (pH ~11) was washed with hexane (500 mL) after which the combined organics were washed with 1 N HCl then water until a pH of 6–7 had been reached. Drying over Na_2SO_4 followed by concentration at <40 °C gave 592 g (92.5%) of light-yellow liquid **5a:** NMR (CCl_3D) δ 0.80–2.00 (m, 28), 2.72 (t, 8, NCH_2); mass spectrum (70 eV) *m/e* 320 (M^+).

Anal. Calcd for $C_{16}H_{36}N_2S_2$: C, 59.94; H, 11.32; N, 8.74; S, 20.00. Found: C, 59.79; H, 11.08; N, 8.62; S, 20.19.

In a manner similar to that for the preparation of **5a**, compounds **5b–g** were synthesized.

Di-*n*-butylaminosulfenyl Chloride (6a). To bis(di-*n*-butylamino) disulfide (**5a**, 40.0 g, 125 mmol, 1 equiv) cooled to −78 °C under a nitrogen atmosphere was added all at once sulfuryl chloride (25.1 g, 188 mmol, 1.5 equiv). The flask was transferred to an ice water bath and allowed to stir at 0–5 °C for 2–3 h after which it was placed under aspirator vacuum followed by high vacuum to give 58.1 g (99%) of foul smelling yellow liquid **6a:** NMR (CCl_3D) δ 0.80–2.00 (m, 14), 3.25 (t, 4, NCH_2). Batch distillation of a sample of the crude product was unsuccessful. The material could be flash distilled (bp 70 °C at 0.4 mm); however, the recovery of product was low.

In a manner similar to that for the preparation of **6a**, compounds **6b–g** were synthesized.

***N*-(di-*n*-butylaminosulfenyl)-*N*-methylcarbamoyl Fluoride (7a) and Methyl Ester 9x.** To a solution of *N*-methylcarbamoyl fluoride (10.0 g, 130 mmol, 1.0 equiv) and di-*n*-butylaminosulfenyl chloride (25.4 g, 130 mmol, 1 equiv) in pyridine (80 mL) at room temperature under a nitrogen atmosphere was added dropwise over 30 min 1,4-diazabicyclo[2.2.2]octane (21.8 g, 195 mmol, 1.5 equiv). Salts began forming as soon as the base was added. The resulting mixture was stirred 4 h beyond the addition time, after which it was poured into a cold (10 °C) mixture of water (160 mL) and hexane (160 mL). The layers were separated and the water (pH ~11) back extracted with cold hexane (80 mL). The combined organics were then washed twice with 1 N HCl (80 mL) and twice with water (80 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator followed by high vacuum to give 22.7 g (74%) of yellow liquid **7a** which had an 82% purity by GLC area percent on 10% OV 17 on Chromosorb W. Distillation of this material gave 18.9 g (61%) of high purity colorless **7a:** bp 84–85 °C (0.20–0.33 mm); $n^{20}D$ 1.4578; IR (thin film) 1780 cm^{-1} (C=O); NMR (CCl_3D) δ 0.80–2.00 (m, 14), 3.15 (bt, 4, NCH_2), 3.30 (s, 3, $CONCH_3$).

Anal. Calcd for $C_{10}H_{21}N_2OSF$: C, 50.82; H, 8.96; N, 11.85. Found: C, 51.15; H, 8.84; N, 11.99.

The material could be converted rapidly (1 h) to the corresponding methyl ester (**9x**) in methanol with triethylamine at room temperature. Compound **9x** was also prepared from methyl *N*-methylcarbamate and di-*n*-butylaminosulfenyl chloride. For **9x:** IR (thin film) 1740 cm^{-1} (C=O); NMR (CCl_3D) δ 0.80–2.00 (m, 14), 3.10 (t, 4, NCH_2), 3.30 (s, 3, $CONCH_3$), 3.70 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 248 (M^+).

In a manner similar to the preparation of **7a**, compounds **7b–g** were prepared (see Table I).

2,3-Dihydro-2,2-dimethyl-7-benzofuranyl *N*-(Di-*n*-butylaminosulfenyl)-*N*-methylcarbamate (9l) (Run No. 3 in Table II). To a vigorously stirred two-phase mixture of 2,3-dihydro-7-hydroxy-2,2-dimethylbenzofuran (1.39 g, 8.47 mmol, 1.0 equiv), sodium hydroxide (0.51 g, 12.71 mmol, 1.5 equiv), tetrabutylammonium hydrogen sulfate (0.29 g, 0.85 mmol, 1.0 equiv), toluene (5 mL), and water (10 mL) was added over 15 min at room temperature a mixture of *N*-(di-*n*-butylaminosulfenyl)-*N*-methylcarbamoyl fluoride (2.00 g, 8.47 mmol, 1.0 equiv) in toluene (5 mL). Analysis of the reaction mixture by GLC after an additional 2 h of stirring indicated none of the fluoride was remaining so the mixture was poured into a separatory funnel containing toluene (10 mL) and water (10 mL). The layers were separated after which the water layer (pH ~11) was washed with toluene (10 mL). The combined organics were washed twice with water (pH of last wash ~6), dried over Na_2SO_4, and concentrated to give 2.75 g (85%) of light-yellow oil which was chromatographed on silica gel to give 2.23 g (69%) of colorless oily **9l:** $n^{20}D$ 1.5116; IR (thin film) 1740 cm^{-1} (C=O); NMR (CCl_3D) δ 0.80–2.00 (m, 14), 1.50 (s, 6, $C[CH_3]_2$), 3.00 (s, 2, ring CH_2), 3.20 (t, 4, NCH_2), 3.40 (s, 3, $CONCH_3$), 6.60–7.10 (m, 3); mass spectrum (70 eV) *m/e* 380 (M^+).

Anal. Calcd for $C_{20}H_{32}N_2O_3S$: C, 63.12; H, 8.48; N, 7.36. Found C, 63.10; H, 8.48; N, 7.05.

Utilizing reactions similar to **9l** above, compounds **9m–w** were prepared (see Table III).

Bis(di-*n*-butylamino) Sulfide (10). To a stirred solution of di-*n*-butylaminosulfenyl chloride (**6a**) (8.00 g, 41 mmol, 1.0 equiv) in diethyl ether (75 mL) under a nitrogen atmosphere at 10 °C was added over 30 min a solution of di-*n*-butylamine (12.14 g, 94 mmol, 2.3 equiv) in ether (25 mL). The resultant mixture was stirred an additional hour, filtered, and concentrated at <40 °C to give 7.83 g (84%) of yellow oily **10:** NMR (CCl_3D) δ 0.80–2.00 (m, 28), 3.00 (t, 8, NCH_2); mass spectrum (70 eV) *m/e* 288 (M^+).

Anal. Calcd for $C_{16}H_{36}N_2S$: C, 66.60; H, 12.58; N, 9.71; S, 11.11. Found: C, 66.85; H, 12.39; N, 9.91; S, 11.36.

Bis(di-*n*-butylamino) Trisulfide (11). To a solution of *bis(di-n*-butylamino) disulfide (**5a**) (16.00 g, 0.05 mol, 1.0 equiv) in hexane (100 mL) at 0 °C under a nitrogen atmosphere was added sulfuryl chloride (6.70 g, 0.05 mol, 1.0 equiv) dropwise over 15 min. The mixture was stirred for 30 min at 0 °C then used below as "solution A".

To a vigorously stirred mixture of hexane (50 mL), water (75 mL), sodium sulfide nonahydrate (14.40 g, 0.06 mol, 1.2 equiv), and sodium hydroxide (1.60 g, 0.04 mol, 0.8 equiv) at 0 °C under a nitrogen at-

mosphere was added dropwise over 30 min "solution A". After the feed, the cooling bath was removed and the mixture was stirred for 1 h. At the end of the reaction period the layers were separated (pH of water ~7) after which the organic layer was washed once with water (50 mL), dried over Na_2SO_4, and concentrated to give 14.75 g (70%) of yellow liquid **11**: NMR (CCl_3D) δ 0.80–2.00 (m, 28), 2.95 (t, 8, NCH_2).

Anal. Calcd for $C_{16}H_{36}N_2S_3$: C, 54.59; H, 10.29; N, 7.94; S, 27.27. Found: C, 53.78; H, 9.52; N, 7.70; S, 28.35.

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Registry No.—**3,** 51229-17-5; **4a,** 111-92-2; **4b,** 110-91-8; **4c,** 142-84-7; **4d,** 103-67-3; **4e,** 14321-27-8; **4f,** 110-89-4; **4g,** 109-89-7; **5a,** 67271-09-4; **5b,** 103-34-4; **5c,** 38126-23-7; **5d,** 62158-05-8; **5e,** 67271-10-7; **5f,** 10220-20-9; **5g,** 15575-30-1; **6a,** 6541-82-8; **6b,** 2958-89-6; **6c,** 34695-15-3; **6d,** 53370-27-7; **6e,** 55285-27-3; **6f,** 16005-90-6; **6g,** 14274-26-1; **9x,** 67271-11-8; **10,** 67271-12-9; **11,** 67271-13-0; HF, 7664-39-3; S_2Cl_2, 10025-67-9; SO_2Cl_2, 7791-25-5; methyl isocyanate, 624-83-9; methyl *N*-methylcarbamate, 6642-30-4.

References and Notes

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(2) L. Black and T. Fukuto, German Patent 2 433 680 (January 1975).
(3) For example, see: (a) E. Kuehle and I. Hammann, German Patent 2 106 300 (August 1972); (b) E. Kuehle, E. Klauke, W. Behren, P. Frahberger, and E. Paul, German Patent 2 041 322 (February 1972); (c) E. Kuehle, E. Klauke, B. Hamburger, and H. Scheinpflug, German Patent 2 243 626 (March 1974).
(4) Shortly after completion of our investigation, Belgian patent applications 843 415 and 843 416 were published which parallel portions of this work.
(5) It is interesting to note that we were unable to carry out the corresponding carbamoyl chloride chemistry. In our hands, *N*-methylcarbamoyl chloride decomposed upon the slightest provocation.
(6) (a) J. Dockx, *Synthesis*, 441 (1973); (b) E. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, 13, 170 (1974).
(7) (a) D. Armitage and C. Tso, *J. Chem. Soc., Chem. Commun.*, 1413 (1971); (b) M. Raban, D. Noyd, and L. Bermann, *J. Org. Chem.*, **40**, 752 (1975).

Notes

Heterocycles in Organic Synthesis. 11.[1] Reactions of Heteroaromatic *N*-Oxides with Pyridine and Diazoles

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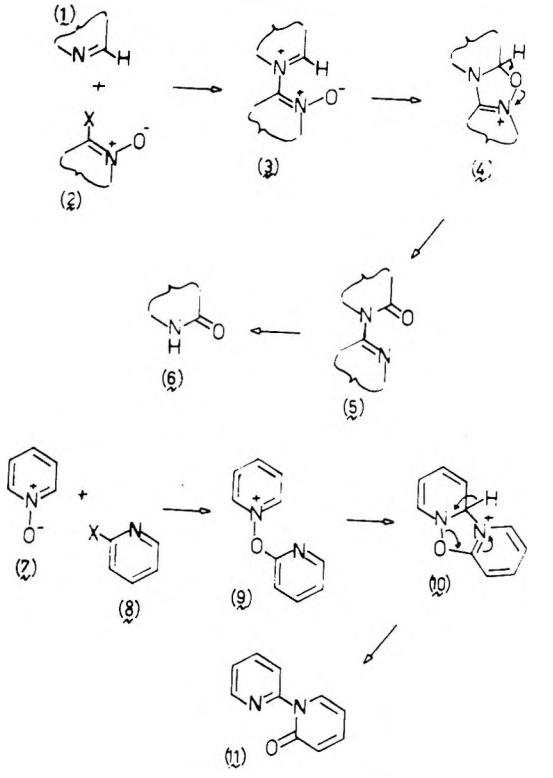
The aim of the present work was to develop a synthetic sequence for the oxidation of heterocyclic nitrogen compounds **1** to the corresponding α-oxo derivatives **6.** Previous methods are inconvenient and/or not general. Direct conversion of pyridine to 2-pyridone requires extreme conditions[2] or conversion to *N*-oxide.[3] Benzimidazole is attacked by most oxidizing agents at the benzene ring,[4] although imidazole itself slowly gives 2-imidazolone with singlet oxygen.[5] Pyrazole is resistant to oxidation.[6]

The reported[7] conversion of pyridine 1-oxide (**7**) to the pyridylpyridone **11** by condensation with a suitably 2-substituted pyridine **8** and intermediates **9** and **10,** led us to consider the reaction sequence **1** + **2** → **6** via intermediates **3, 4,** and **5** (Scheme I).

Scheme I



Experiments with 2-Chloro-5-nitropyridine 1-Oxide (12) as Compound 2. This oxide possesses a reactive chlorine atom and readily formed substitution products with aniline (**13,** R = NHPh) and piperidine [**13,** R = $N(CH_2)_5$] (Scheme II). Pyrazole also gave the expected product **14,** but this was stable to heat and sublimed unchanged: with acetic anhydride an acetoxy group was introduced into the 6 position of the pyridine ring to give **15** by a known[8] reaction, leaving the pyrazole ring unaffected.

Imidazole readily formed **16,** which was again stable to heat and also sublimed unchanged. It was converted by acetic anhydride to **17,** which was also obtained directly from **12** by Ac_2O treatment. The structure of **17** was confirmed by hydrolysis to the known[9] 1-hydroxy-2-pyridone **18.** Methyl tosylate with **16** gave **19** (X = OTs), whereas **19** (X = Cl) was obtained by direct reaction of **12** and methylimidazole. The salts **19** (X = Cl or OTs) gave an inseparable mixture after prolonged heating in the presence of a hindered base.

Attempted reaction of **12** with pyridine did not succeed. With pyridine 1-oxide, the product was **20** (Scheme II), apparently formed by the reaction of **12** with itself followed by reduction and hydrolysis. This structure of **20** was based on analytical, mass spectral, IR, and NMR data; attempts to synthesize **20** by reaction of 2-chloro-5-nitropyridine with **18,** or the sodium salt of **18,** failed.

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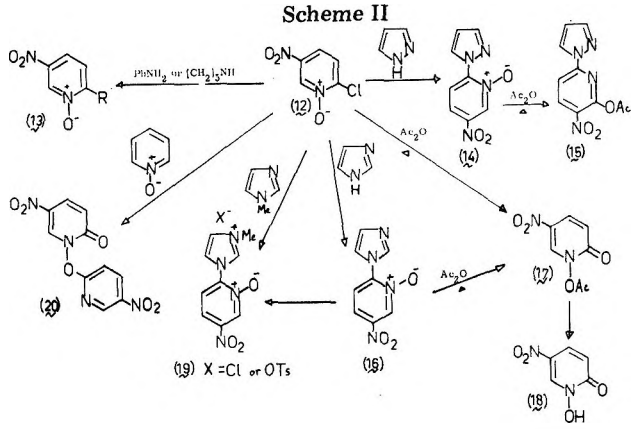
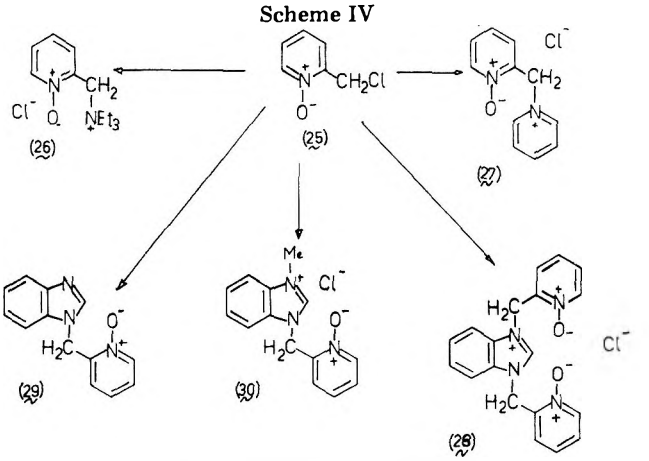
Scheme II



Scheme IV



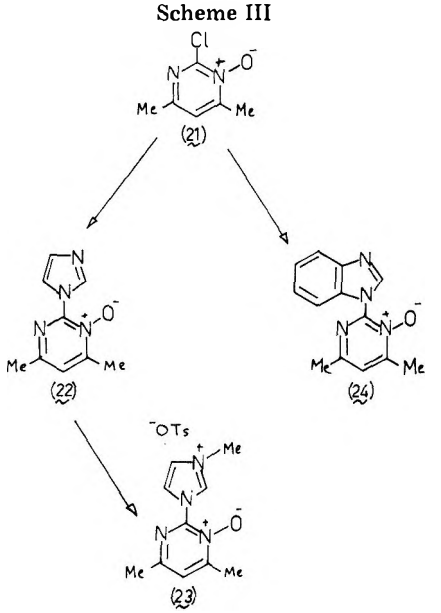
Experiments with 2-Chloro-4,6-dimethylpyrimidine 1-Oxide (21) as Compound 2. Imidazole reacted with the oxide **21** to form the expected product **22** (Scheme III), which was recovered unchanged after sublimation or after prolonged heating in the presence of a hindered base. With benzimidazole, the oxide **21** gave **24,** which also sublimed unchanged. Methylation of the imidazole **22** gave **23,** but the methyl derivative did not react smoothly with bases under various conditions.[10]

Experiments with 2-(Chloromethyl)pyridine 1-Oxide (25) as Compound 2. This benzylic type chlorine of **25** is known to be displaced by various nucleophiles[11] and **25** has been used to introduce the 2-picolyl 1-oxide group into substrates,[12] where it has been used to protect amino functions.[13] Removal should also be easy.[14] As expected, the *N*-oxide **25** readily reacted with triethylamine to give **26** (Scheme IV). With pyridine, **25** gave **27,** 1-methylbenzimidazole similarly formed **30,** and isoquinoline formed the corresponding quaternary salt, whereas benzimidazole itself, although yielding some of the monoadduct **29,** mainly underwent a double reaction to yield **28.** Salt **28** is very hygroscopic and normal samples display ν(OH) at 3380 cm^{-1}; and proton NMR signal for the 2CH at δ 10.3 is rapidly exchanged for deuterium by shaking with D_2O (cf. ref 15, 16). 1-Benzyl-3-methylbenzimidazolinium cation (but not 2-benzylisoquinolinium cation) also underwent rapid hydrogen exchange under similar conditions.

All attempts to transfer the *N*-oxide oxygen atoms of species **27–30,** and the analogous cation formed from isoquinoline, to the other heterocyclic ring failed.[17]

Conclusions. We believe that the failure to achieve reaction sequences of type **3** → **6** is due to difficulty with the proton abstraction step **4** → **5** and are therefore now exploring reagents in which such proton transfer can be achieved intramolecularly.

Scheme III



Experimental Section

^1H NMR spectra were recorded with Varian HA-100 and Perkin-Elmer R 12 spectrometers (Me_4Si as internal standard), IR spectra with a Perkin-Elmer 257 spectrometer, and mass spectra with a Hitachi Perkin-Elmer spectrometer.

The following compounds were prepared by literature methods. 2-Chloro-5-nitropyridine: needles, 88.5%, mp 107 °C (MeOH; lit.[18] mp 106 °C). 2-Chloro-5-nitropyridine 1-oxide: needles, 54%, mp 137 °C (CH_2Cl_2–Et_2O; lit.[19] mp 137–139 °C). 1-Methylbenzimidazole: plates, 61%, mp 60 °C, bp 168 °C (20 mm) [lit.[20] bp 183–185 °C (37 mm)]. 1-Methylimidazole, 51%, bp 99 °C (18 mm) [lit.[21] bp 97 °C (18 mm)]. 2-Chloro-4,6-dimethylpyrimidine: 74%, bp 64–66 °C (2 mm), mp 38 °C (lit.[22] mp 38 °C). 2-Chloromethylpyridine: 45%, bp 45–47 °C (1.5 mm) [lit.[23] bp 45–47 °C (1.5 mm)]. 2-Chloromethylpyridine 1-oxide (**26**): 98%, needles from benzene, mp 74–75 °C (lit.[12] mp 75 °C).

2-Anilino-5-nitropyridine 1-Oxide (13, R = NHPh). Aniline (0.213 g), 2-chloro-5-nitropyridine 1-oxide (**12**) (0.20 g), and CH_2Cl_2 (3 mL) were stirred for 12 h at 20 °C. The solvent was evaporated under reduced pressure and the residue crystallized from EtOH to give the 1-oxide **13** (R = NHPh) as needles (0.160 g, 60%): mp 186 °C.

Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.1; H, 3.9; N, 18.3; M, 241. Found: C, 57.0; H, 4.0; N, 18.2; M^+·, 241.

5-Nitro-2-piperidiniopyridine 1-Oxide [13, R = N(CH$_2$)$_5$]. Piperidine (0.195 g) in CH_2Cl_2 (5 mL) was added to 2-chloro-5-nitropyridine 1-oxide (0.2 g) in CH_2Cl_2 (5 mL) and stirred at 20 °C for 1 h. The solvent was evaporated to give the 1-oxide **13** [R = $NH(CH_2)_5$] as needles (0.152 g, 60%): mp 149 °C (from light petroleum bp 80–100 °C).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.8; H, 5.9; N, 18.8; M, 223. Found: C, 53.7; H, 5.8; N, 18.5; M^+·, 223.

5-Nitro-2-(1-pyrazolyl)pyridine 1-Oxide (14). 2-Chloro-5-nitropyridine 1-oxide (0.2 g), pyrazole (0.156 g), and toluene (15 mL) were heated under reflux for 4 h and then left for 12 h. The 1-oxide crystallized as needles (0.18 g, 76%): mp 174 °C (from CH_2Cl_2–Et_2O); IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H NMR [100 MHz, $(CD_3)_2SO$] δ 9.35 (d, 1 H, J = 1 Hz), 9.24 (m, 1 H), 8.27 (m, 2 H), 8.03 (d, 1 H, J = 1 Hz), 6.68 (m, 1 H).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.6; H, 2.9; N, 27.2; M, 206. Found: C, 46.4; H, 3.2; N, 26.6; M^+·, 206.

6-Acetoxy-5-nitro-2-(1-pyrazolyl)pyridine (15). 5-Nitro-2-(1-pyrazolyl)pyridine 1-oxide (0.206 g) and Ac_2O (25 mL) were heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue crystallized from MeOH to give needles of the 6-acetoxypyridine (0.17 g, 58%): mp 140 °C; IR (Nujol) 1775 (C=O), 1200 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 8.65 (d, 1 H, J = 6 Hz), 8.5 (d, 1 H, J = 2 Hz), 8.05 (d, 1 H, J = 6 Hz), 7.82 (s, 1 H), 6.52 (m, 1 H), 2.45 (s, 3 H).

Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.4; H, 3.3; N, 22.6. Found: C, 48.1; H, 3.4; N, 22.9.

2-(1-Imidazolyl)-5-nitropyridine 1-Oxide (16). 2-Chloro-5-nitropyridine 1-oxide (0.2 g), imidazole (0.156 g), and MeCN (15 mL) were heated under reflux for 4 h and kept for 12 h. The 1-oxide separated from MeCN as needles (0.24 g, 93%): mp 215 °C; IR (Nujol)

1260 cm^{-1} (N^+–O^-); ^1H NMR [100 MHz, $(CD_3)_2SO$] δ 9.26 (d, 1 H, J = 1 Hz), 8.60 (s, 1 H), 8.26 (dd, 1 H, J = 1.5, J_o = 5 Hz), 8.04 (d, 1 H, J = 5 Hz), 7.90 (s, 1 H), 7.18 (s, 1 H).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.6; H, 2.9; N, 27.2; M, 206. Found: C, 46.0; H, 2.9; N, 26.6; M^+·, 206.

1-Acetoxy-5-nitro-2-pyridone (17). Method a. 2-Chloro-5-nitropyridine 1-oxide (0.349 g) was heated in Ac_2O (3 mL) at 140 °C for 1.5 h. Solvent was removed under reduced pressure and the residue crystallized from MeOH to give the 2-pyridone as needles (0.265 g, 67%): mp 161–163 °C; IR (Nujol) 1817, 1692 cm^{-1} (C=O); ^1H NMR [100 MHz, $(CD_3)_2SO$] δ 9.58 (d, 1 H, J = 1.5 Hz), 8.24 (dd, 1 H, J_m = 1.5, J_o = 5.5 Hz), 6.76 (d, 1 H, J = 5.5 Hz), 2.38 (s, 3 H).

Anal. Calcd for $C_7H_6N_2O_5$: C, 42.4; H, 3.1; N, 14.2. Found: C, 42.1; H, 3.2; N, 14.1.

Method b. 2-(1-Imidazolyl)-5-nitropyridine 1-oxide (0.1 g) was heated under reflux in Ac_2O (5 mL) for 1 h and cooled. Ice water (15 ml) was added and the product extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ extracts were washed with H_2O (10 mL), dried (K_2CO_3), and evaporated. Crystallization of the residue from MeOH gave the pyridone as needles (0.031 g, 30%): mp 162 °C; IR (Nujol) 1817, 1692 cm^{-1} (C=O).

1-Hydroxy-5-nitro-2-pyridone (18). 1-Acetoxy-5-nitro-2-pyridone (0.198 g), NaOH (0.04 g), and H_2O (10 mL) were stirred at 20 °C for 2 h and then acidified with HCl. The product was extracted with $CHCl_3$ (3 × 10 mL) and the extracts were dried ($MgSO_4$) and evaporated to give the hydroxypyridone (0.125 g, 80%): mp 180°C (lit.[9] mp 188 °C); IR (Nujol) 3200–3060 (OH), 1670 cm^{-1} (C=O); ^1H NMR [100 MHz, $(CD_3)_2SO$] δ 9.21 (d, 1 H, J = 1.5 Hz), 8.14 (dd, 1 H, J_m = 1.5, J_o = 5.5 Hz), 6.60 (d, 1 H, J = 5.5 Hz).

Anal. Calcd for $C_5H_4N_2O_4$: C, 38.4; H, 2.6. Found: C, 38.2; H, 2.9.

1-Methyl-3-(5-nitro-1-oxido-2-pyridyl)imidazolium *p*-Toluenesulfonate (19, X = OTs). 2-(1-Imidazolyl)-5-nitropyridine 1-oxide (0.432 g), methyl *p*-toluenesulfonate (0.744 g), and MeCN (50 mL) were heated under reflux for 30 h. The *p*-toluenesulfonate (0.595 g, 74%) crystallized from MeCN as plates: mp 212 °C; IR (Nujol) 1265 cm^{-1} (N^+–O^-); ^1H NMR (60 MHz, CF_3CO_2H) δ 9.8 (s, 1 H), 9.62 (s, 1 H), 8.65 (s, 1 H), 8.45 (s, 1 H), 8.1 (s, 1 H), 7.88 (s, 1 H), 7.82 (d, 2 H, J = 6 Hz), 7.38 (d, 2 H, J = 6 Hz), 4.2 (s, 3 H), 2.45 (s, 3 H).

Anal. Calcd for $C_{16}H_{16}N_4O_6S$: C, 49.0; H, 4.1; N, 14.3. Found: C, 48.9; H, 4.3; N, 14.3.

1-Methyl-3-(5-nitro-1-oxido-2-pyridyl)imidazolium Chloride (19). 2-Chloro-5-nitropyridine 1-oxide (**12**, 0.175 g) and *N*-methylimidazole (0.082 g) were kept at 20 °C for 48 h. The solid obtained was washed with $(CH_2)_4O$ (2 × 20 mL) and recrystallized from MeOH–Et_2O to give the chloride **19** as plates (0.120 g, 53%): mp 228–230 °C; IR (Nujol) 1265 cm^{-1} (N^+–O^-); ^1H NMR (CF_3CO_2H) δ 9.75 (s, 1 H), 9.65 (s, 1 H), 8.78 (d, 1 H), 8.35 (d, 1 H), 8.1 (s, 1 H), 7.75 (s, 1 H), 4.25 (s, 3 H).

Anal. Calcd for $C_9H_9ClN_4O_3$: C, 42.1; H, 3.6; N, 21.9. Found: C, 42.4; H, 3.7; N, 21.8.

5-Nitro-1-(5-nitro-2-pyridyloxy)-2-pyridone (20). 2-Chloro-5-nitropyridine 1-oxide (0.349 g) in toluene (25 mL) was added to pyridine 1-oxide (0.190 g) in toluene (10 mL), heated under reflux for 3 h, and then set aside for 12 h. A dark oil which deposited was removed and the solution concentrated to give the pyridone (0.043 g, 6%) as needles from toluene: mp 247 °C; IR (Nujol) 1680 (C=O), 1560, 1350 cm^{-1} (NO_2); ^1H NMR [100 MHz, $(CD_3)_2SO$] δ 9.25 (dd, 2 H, J_m = 1.5, J_o 5.5 Hz), 8.1–8.3 (m, 3 H), 6.7 (d, 1 H, J = 5.5 Hz).

Anal. Calcd for $C_{10}H_6N_4O_6$: C, 43.2; H, 2.2; N, 20.1; M, 270. Found: C, 43.3; H, 2.0; N, 19.6; M^+·, 270.

2-Chloro-4,6-dimethylpyrimidine 1-Oxide (21). Maleic anhydride (24 g) in $CHCl_3$ (80 mL) was treated with 30% H_2O_2 (3.4 g) at 0–5 °C, and the mixture was stirred for 2 h at 0–5 °C. 2-Chloro-4,6-dimethylpyrimidine (1.43 g) was added and set aside for 5 days at 10 °C. Maleic acid (17 g) was filtered off. The $CHCl_3$ solution was washed with aqueous K_2CO_3 (10%, 4 × 20 mL), dried (K_2CO_3), and evaporated at 30 °C (20 mm Hg). The semisolid residue was extracted with boiling light petroleum (bp 60–80 °C, 3 × 40 mL). Extracts were evaporated to 80 mL and the *N*-oxide separated from light petroleum as needles (0.53 g, 34%): mp 97 °C; IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H NMR ($CDCl_3$) δ 7.15 (s, 1 H), 2.60 (s, 3 H), 2.50 (s, 3 H).

Anal. Calcd for $C_6H_7ClN_2O$: C, 45.4; H, 4.5; N, 17.7. Found: C, 45.7; H, 4.5; N, 17.4.

4,6-Dimethyl-2-(1-imidazolyl)pyrimidine 1-Oxide (22). Imidazole (0.294 g) and 2-chloro-4,6-dimethylpyrimidine 1-oxide (0.343 g) in MeCN (15 mL) were heated under reflux for 6 h. The solvent was evaporated under reduced pressure and the residue extracted with boiling benzene (2 × 20 mL). The extracts on evaporation gave the 1-oxide as a residue (0.293 g, 71%) which formed needles from light petroleum (bp 80–100 °C); mp 154 °C; IR (Nujol) 1260 cm^{-1} N^+–O^-); ^1H NMR (60 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 8.25 (s, 1 H), 7.17 (d, 2 H, J = 3 Hz), 2.16 (s, 3 H), 2.58 (s, 3 H).

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.8; H, 5.3; N, 29.5; M, 190. Found: C, 56.8; H, 5.4; N, 29.1; M^+·, 190.

1-Methyl-3-(4,6-dimethyl-1-oxidopyrimidin-2-yl)imidazolium *p*-Toluenesulfonate (23). 4,6-Dimethyl-2-(1-imidazolyl)pyrimidine 1-oxide (**22**, 0.575 g), methyl *p*-toluenesulfonate (0.570 g), and MeCN (40 mL) were heated under reflux for 30 h. The solvent was evaporated under reduced pressure and the residue washed with hot $(CH_2)_4O$ (3 × 10 mL) giving the *p*-toluenesulfonate **23** as rods (0.981 g, 82%): mp 170 °C (from MeOH–Et_2O); IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H NMR ($CDCl_3$) δ 10.31 (s, 1 H), 8.29 (s, 1 H), 7.96 (s, 1 H), 7.65 (d, 2 H), 7.31 (s, 1 H), 7.01 (d, 2 H), 4.11 (s, 3 H), 2.47 (s, 6 H), 2.34 (s, 3 H).

Anal. Calcd for $C_{17}H_{20}N_4O_4S$: C, 54.2; H, 5.4; N, 14.9. Found: C, 54.0; H, 5.1; N, 15.0.

2-(1-Benzimidazolyl)-4,6-dimethylpyrimidine 1-Oxide (24). 2-Chloro-4,6-dimethylpyrimidine 1-oxide (0.23 g) and benzimidazole (0.18 g) were heated under reflux in $(CH_2)_4O$ (10 mL) for 6 h. Benzimidazole hydrochloride was filtered off and the filtrate was evaporated. The residue was extracted with benzene (3 × 10 mL) and the extracts concentrated to give the *N*-oxide (0.16 g, 46%) which separated from benzene as plates: mp 174 °C; IR (Nujol) 1250 cm^{-1} (N^+–O^-); ^1H NMR (60 MHz) ($CDCl_3$) δ 9.81 (s, 1 H), 8.01 (m, 2 H), 7.22 (m, 2 H), 2.60 (s, 3 H), 2.58 (s, 3 H).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 22.3; M, 240. Found: C, 64.7; H, 5.1; N, 22.6; M^+·, 240.

1-(1-Oxido-2-pyridylmethyl)pyridinium Chloride (27). 2-Chloromethylpyridine 1-oxide **25** (1.15 g) and pyridine (1.30 g) were heated under reflux in MeCN (80 mL) for 24 h. The solvent was removed at 80 °C (15 mm Hg) and the residue washed with hot Et_2O (2 × 50 mL) leaving the solid highly hygroscopic chloride **27** (1.77 g, 98%), mp 215–220 °C, which crystallized as needles (from EtOH–Et_2O): mp 220–222 °C; IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H NMR [$(CD_3)_2SO$] δ 6.1 (s, 2 H), 7.4 (m, 2 H), 8.0–8.3 (m, 4 H), 8.6 (m, 1 H), 9.3 (d, 2 H, finely split, J = 6, J = 1 Hz); *m/e* 187 (M^+ − Cl). The compound was characterized as the dipicrate as yellow needles: mp 142–143 °C (from EtOH) (lit.[24] 142–143 °C).

Anal. Calcd for $C_{11}H_{12}N_2O\cdot[(NO_2)_3C_6H_2O]_2$: C, 42.9; H, 2.5; N, 17.4. Found: C, 42.8; H, 2.6; N, 17.4.

1-(1-Oxido-2-pyridylmethyl)-3-methylbenzimidazolium Chloride (30). 1-Methylbenzimidazole (1.32 g) and the 1-oxide **25** (0.72 g) were heated under reflux in MeCN (50 mL) for 24 hr. MeCN was removed at 80 °C (15 mm Hg) to give the chloride **30** (1.02 g, 74%) which separated from EtOH–Et_2O as prisms: mp 217–221 °C; IR ($CHBr_3$) 1255 cm^{-1} (N^+–O^-); ^1H NMR [$(CD_3)_2SO$] δ 4.2 (s, 3 H), 6.0 (s, 2 H), 7.4–7.8 (m, 4 H), 7.9–8.5 (m, 4 H), 10.2 (s, 1 H); *m/e* 240 (M^+ − Cl).

The salt was characterized as the perchlorate which crystallized as flakes (from EtOH); mp 212.5–214 °C.

Anal. Calcd for $C_{14}H_{14}ClN_3O_5$: C, 49.5; H, 4.2; N, 12.4. Found: C, 49.1; H, 4.2; N, 12.6.

2-(1-Oxido-2-pyridylmethyl)isoquinolinium Chloride. Isoquinoline (2.10 g) and the 1-oxide **25** (1.15 g) were heated under reflux in MeCN (80 mL) for 24 h. Solvent was removed at 80 °C (15 mmHg) and the residue washed with hot EtOAc (2 × 25 mL); the residual chloride (2.10 g, 95%), crystallized from EtOH–Et_2O as greenish needles: mp 183–185 °C; IR ($CHBr_3$) 1650 (C=N), 1265 cm^{-1} (N^+–O^-); ^1H NMR [$(CD_3)_2SO$] δ 6.1 (s, 2 H), 7.5 (m, 2 H), 7.9–8.6 (m, 7 H), 8.9 (d, 1 H, finely split, J = 7, J = 1 Hz), 10.3 (s, 1 H, finely split, J = 1 Hz); *m/e* 237 (M^+ − Cl).

The salt was characterized as the perchlorate, which crystallized as fine needles (from EtOH): mp 157–158 °C; IR ($CHBr_3$) 1650 (C=N), 1260 (N^+–O^-), 1080 cm^{-1} (ClO).

Anal. Calcd for $C_{15}H_{13}N_2O\cdot ClO_4$: C, 53.5; H, 3.9; N, 8.3. Found: C, 53.8; H, 4.1; N, 8.1.

1,3-Di(1-oxido-2-pyridylmethyl)benzimidazolium Chloride (28). Benzimidazole (0.236 g) and the 1-oxide **25** (0.585 g) were heated under reflux in MeCN (40 mL) for 40 h. Volatiles were removed at 80 °C (15 mmHg) and the residual oil washed with hot Et_2O (2 × 50 mL), leaving the solid chloride **28** (0.783 g, 94%), which crystallized as flakes: mp 250–252 °C (from EtOH–Et_2O); IR (Nujol) 1260 cm^{-1} (N^+–O^-); ^1H (NMR) [$(CD_3)_2SO$] δ 6.2 (s, 2 H), 7.5–8.6 (m, 12 H), 10.3 (s, 1 H); *m/e* 333 (M^+ − Cl).

Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.7; H, 4.9; N, 15.2; Cl, 9.6. Found: C, 61.4; H, 4.8; N, 14.6; Cl, 9.8.

1-(1-Oxido-2-pyridylmethyl)benzimidazole (29). The 1-oxide **25** (0.90 g) in EtOH (10 mL) was added dropwise during 1 h with stirring to benzimidazole (1.50 g) and K_2CO_3 (2.0 g) in EtOH (10 mL) at 0 °C. The solution was stirred for 72 h at 20 °C. Potassium chloride was filtered off and the solvent removed at 80 °C (15 mm). The oily residue was dissolved in hot EtOAc (20 mL); on cooling, the *N*-oxide **29** (1.13 g, 81%) separated and was recrystallized from EtOAc to give

needles: mp 166–167 °C; IR ($CHBr_3$) 1250 cm^{-1} ($N^+–O^-$); ^1H NMR ($CDCl_3$) δ 5.8 (s, 2 H), 6.8 (d, 1 H, J = 2 Hz), 7.2–7.4 (m, 5 H), 8.1 (m, 1 H), 8.2 (s, 1 H), 8.5 (dd, 1 H, J = 6, J = 1 Hz); m/e 225 (M^+).

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.1; H, 4.9; N, 18.9.

The *N*-oxide **29** gave the corresponding 3-methylperchlorate **30** by methylation and conversion to the perchlorate, which crystallized as flakes (from EtOH): mp 212–214 °C.

***N*-(1-Oxido-2-pyridylmethyl)triethylammonium Chloride (26).** Et_3N (0.500 g) and the 1-oxide **25** (0.360 g) were heated under reflux in MeCN (40 mL) for 24 h. MeCN was evaporated 80 °C (15 mmHg) and the residue was washed with hot Et_2O (2 × 20 mL) leaving the chloride **27** (0.590 g, 96%), which separated from EtOH–Et_2O as prisms: mp 194–196 °C; IR (Nujol) 1260 cm^{-1} ($N^+–O^-$); ^1H NMR [$(CD_3)_2SO$] δ 1.1 (t, 9 H, J = 8 Hz), 3.2 (q, 9 H, J = 8 Hz), 4.6 (s, 2 H), 7.2–7.6 (m, 2 H), 7.8 (dd, 1 H, J = 8 Hz, J = 1 Hz), 8.3 (dd, 1 H, J = 6, J = 1 Hz).

The salt was characterized as the dipicrate, which crystallized from EtOH as yellow needles: mp 120.5–122 °C.

Anal. Calcd for $C_{12}H_{22}N_2O·[(NO_2)_3C_6H_2O]_2$: C, 43.3; H, 3.9; N, 16.8. Found: C, 43.4; H, 4.0; N, 16.8.

1-Benzyl-3-methylbenzimidazolium Bromide. 1-Methylbenzimidazole (1.32 g) and benzyl bromide (1.71 g) were stirred in EtOAc (20 mL) for 24 h. The precipitated bromide (1.70 g, 56%) crystallized from EtOH–Et_2O as prisms: mp 78–80 °C; ^1H NMR [$(CD_3)_2SO$] δ 4.1 (s, 3 H), 5.8 (s, 2 H), 7.3–8.1 (m, 9 H), 10.3 (s, 1 H). The salt was characterized as the perchlorate rods (from EtOH): mp 146–147.5 °C; IR ($CHBr_3$) 1650 (C=N), 1080 cm^{-1} (ClO).

Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.8; H, 4.7; N, 8.7. Found: C, 55.9; H, 4.9; N, 8.3.

2-Benzylisoquinolinium Bromide. Isoquinoline (1.29 g) and benzyl bromide (1.71 g) were heated under reflux in MeCN (25 mL) for 3 h. Solvent was removed at 80 °C (15 mm), and the residual bromide (2.83 g, 94%) crystallized from EtOH–Et_2O as needles: mp 108–110 °C (lit.[25] mp 110–111.5 °C); ^1H NMR [$(CD_3)_2SO$] δ 6.1 (s, 2 H), 7.3–7.8 (m, 5 H), 7.9–8.4 (m, 4 H), 8.6 (d, 1 H), 9.0 (d, 1 H), 10.7 (s, 1 H, finely split, J = 1 Hz).

The corresponding perchlorate crystallized from EtOH as prisms: mp 170–172 °C (lit.[25] mp 167–168 °C).

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Registry No.—**12,** 13198-73-7; **13** (R = NHPh), 66809-32-3; **13** [R = $N(CH_2)_5$], 66809-33-4; **14,** 66809-34-5; **15,** 66809-35-6; **16,** 66809-36-7; **17,** 66809-37-8; **18,** 45939-70-6; **19** (X = OTs), 66809-39-0; **19** (X = Cl), 66809-40-3; **20,** 66809-41-4; **21,** 66809-42-5; **22,** 66809-43-6; **23,** 66809-45-8; **24,** 66809-46-9; **25,** 31640-94-5; **26,** 31640-96-7; **26** dipicrate, 66809-49-2; **27,** 66809-50-5; **27** dipicrate, 66809-53-8; **28,** 66809-54-9; **29,** 66809-55-0; **30,** 66809-56-1; **30** perchlorate, 66809-58-3; aniline, 62-53-3; piperidine, 110-89-4; pyrazole, 288-13-1; imidazole, 288-32-4; *N*-methylimidazole, 616-47-7; pyridine 1-oxide, 694-59-7; 2-chloro-4,6-dimethylpyrimidine, 4472-44-0; benzimidazole, 51-17-2; isoquinoline, 119-65-3; 1-methylbenzimidazole, 1632-83-3; 2-(1-oxido-2-pyridylmethyl)isoquinolinium chloride, 66809-59-4; 2-(1-oxido-2-pyridylmethyl)isoquinolinium perchlorate, 66809-61-8; 1-benzyl-3-methylbenzimidazolium bromide, 66809-62-9; 1-benzyl-3-methylbenzimidazolium perchlorate, 66809-77-6; benzyl bromide, 100-39-0; 2-benzylisoquinolinium bromide, 23277-04-5; pyridine, 110-86-1.

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D-Homoandrostanes. 3. Incubation of Some *D*-Homo-5α-androstanes with *Aspergillus ochraceus*[1a]

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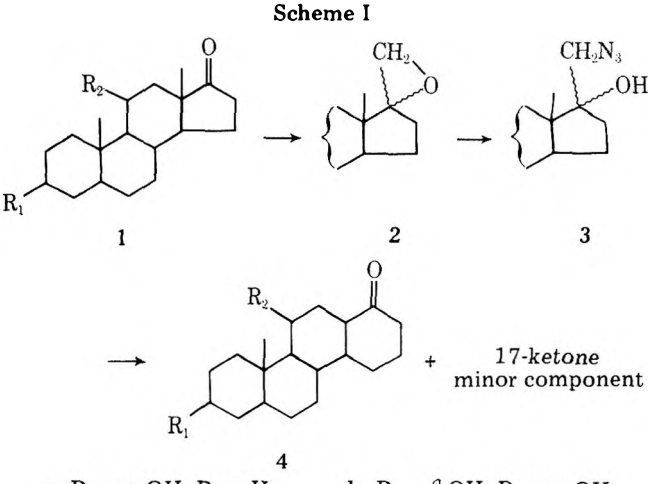
In preparing *D*-homo-5α-androstanes[2] our intention was to determine the effect of increase in terminal ring size on the course of microbiological hydroxylation as compared with that of normal steroids. For part of these studies we chose the microorganism *Aspergillus ochraceus,* which has been extensively documented[3] as an 11α-hydroxylator of steroids with very occasional transformations at C(1),[4] C(6),[5] and C(7).[5] Work with cell-free cultures of this microorganism has demonstrated[6] that two independently acting hydroxylase enzymes are responsible for the 11α- and 6β-hydroxylations.

Table I presents the times of incubation, the amount of starting material recovered, and the observed modifications of the steroid substrates, which have, with certain exceptions, been synthesized previously.[2]

3α-Hydroxy-*D*-homo-5α-andostan-17α-one[7] was prepared according to the established route (Scheme I, **1a** → **4a**). The two, 3,11-dioxygenated steroids were prepared from the

Scheme I



a, R_1 = α-OH, R_2 = H_2; **b**, R_1 = β-OH; R_2 = α-OH

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Table I

substrate	registry no.	incubation, days	starting material recovered, %	reaction and % conversion[a]	registry no.
3-ketone	39851-65-5	4	>90	none observed	
Δ^4-3-ketone	51057-29-5	4	8	11α,6β-diOH, 14; 11α,6β-diOH → 11α-OH,6-C=O, 19	62193-74-2
3,6-diketone	61231-98-9	4.5	50	11α-OH, 29	62193-61-7
3,7-diketone	61232-04-0	6	24	11α-OH, 20	62193-62-8
3,11-diketone	62193-54-8	4	10	none observed	
11α-hydroxy-3-ketone	62193-43-5	4	85	none observed	
3,17a-diketone	61231-79-6	4	0	11α-OH, 73	66966-81-2
3,17-diketone	20377-71-3	4.5	24	11α-OH, 79	62193-63-9
2,17a-diketone	61231-93-4	6	61	11α-OH, 65	66966-82-3
3β-hydroxy-17a-ketone	26729-16-8	5	38	11α-OH, 46; 11α-OH, 3β-OH → 11α-OH,3-C=O, 41	66966-83-4
3α-hydroxy-17a-ketone	62193-42-4	5	33	11α-OH, 48	62193-71-9
Δ^5-3β-hydroxy-17a-ketone	3278-99-7	5	43	11α-OH, 35	56103-43-6

[a] Conversion is calculated after subtracting starting material, assuming remainder is all converted steroid.

product of the ring expansion of 3β,11α-dihydroxy-5α-androstan-17-one[5] (**1b**) by reduction to the diol and appropriate oxidation. The procedure involved in determining the site of hydroxylation depends a great deal on spectroscopic examination of the modified steroid and its oxidation products, and is best illustrated for 3β-hydroxy-*D*-homo-5α-androstan-17a-one. The microbially transformed steroid was shown to be a dihydroxylated ketone both by elemental analysis and by the appearance of an additional one-proton signal at τ 6.00 in the NMR. Calculation of the expected chemical shift positions of the C(18) and C(19) methyl groups in $CDCl_3$ using values obtained by Zürcher[8] for the different possible positions of the introduced hydroxyl group, and in the derived triketone by oxidation for the "new" carbonyl group, and comparison with the observed values, gives the site and orientation of microbial attack as C(11α). This method depends on the additivity of shifts due to different structural features in one solvent and is augmented by calculations on shifts caused by change of solvent from $CDCl_3$ to benzene[9] for the triketone.

In order to apply the above method, various *D*-homoandrostanes were prepared and their methyl chemical shifts were measured in $CDCl_3$ solution.[10] This permitted us to determine the substituents effects. For keto steroids the information was extended to measurement of solvent shift values for the different carbonyl groups. The structure of the product **4b** was obtained by incubating 3β-hydroxy-5α-androstan-17-one with *Aspergillus ochraceus*[5] and subjecting the incubation product to the ring expansion procedure (**1b** → **4b**). In addition both materials gave the known 3,11,17a-trione[11] on oxidation.

The products of the other incubations were identified by simple chemical conversion and application of the spectroscopic method as outlined above, as mono-11α-hydroxylated steroids, in keeping with the known behavior of the microorganism. For the 3,11-diketone, hydroxylation is effectively blocked by the 11-keto group, while the lack of 6β-hydroxylation in the 3-keto-11α-hydroxy steroid is surprising as this molecule might have been expected to induce the responsible hydroxylase,[6] which is clearly functioning for the Δ^4-3-ketone. Here a second product owing to isomerization of the 6β-hydroxy-4-en-3-one system to the 3,6-dione was isolated. Such isomerization has been observed under acidic[5] and basic[12] conditions.

As a general observation, the ring D homologation leads to a lower conversion compared with those of the normal series analogues. Such effects might be tentatively attributed to the combined effects of differences in solubility as well as molecular geometry and flexibility.

Experimental Section

General directions have been described previously.[2]

3α-Hydroxy-*D*-homo-5α-androstan-17a-one (4a) and 3β,11α-Dihydroxy-*D*-homo-5α-androstan-17a-one (4b). Sodium hydride (50% in oil, 2 g) was washed with dry benzene and added in portions to a stirred suspension of 12 g of trimethyloxosulfonium iodide in 40 mL of dimethylformamide under nitrogen. After evolution of hydrogen, 3 g of 3α-hydroxy-5α-androstan-17-one (**1a**) was added and stirring continued until TLC analysis by green spot formation in iodine vapor and lack of carbonyl absorption in the IR indicated completion of the reaction. Addition of water and extraction with ethyl acetate gave a quantitative yield of spirooxiranes **2a:** IR 3610, 3430, 1023, 850 cm^{-1}; NMR τ 9.18 (CH_3-19 and CH_3-18 of 17 α-oxirane), 9.11 (CH_3-18 of 17β-oxirane), 7.39 and 7.07 (2d, J = 5 Hz, H-20), 5.90 (m, $W_{1/2}$ = 8 Hz, H-3).

In a similar manner **1b**[13] (3 g from an incubation as described in the third experiment) was converted to spirooxirane mixture **2b:** IR 3600, 3400, 1030 cm^{-1}; NMR τ 9.13 (CH_3-18 of 17α-oxirane), 9.08 (CH_3-18 of 17β-oxirane), 9.03 (CH_3-19), 7.40 (m, oxirane protons), 4.60–4.00 (m, H-3 and H-11).

The spirooxiranes **2a** (3g) in 100 mL of dimethylformamide were heated at reflux temperature with 2 g of sodium azide and 2 g of boric acid for 3 h. Dilution with water and extraction with ethyl acetate gave a 98% yield of hydroxy azides **3a**. The dihydroxy azide **3b** was prepared in a similar manner. Both had the characteristic azide absorption at 2100 cm^{-1} in the IR.

The crude epimeric hydroxy azides **3a** were dissolved in 25 mL of acetone and acidified to pH 1–2 with concentrated hydrochloric acid and treated with 2 g of zinc powder added in small portions. After hydrogen evolution had ceased the remaining zinc was filtered out and washed with acetone. The combined filtrates were diluted with 120 mL of water and extracted with ether to remove neutral components. The stirred aqueous layer, cooled to below 5 °C, was treated with 3 g of sodium nitrite during 30 min. After 4 h at this temperature extraction with ethyl acetate gave a mixture of 1 g of 17a- and 17-ketones as an oil, from which was isolated only 0.8 g of 3α-hydroxy-*D*-homo-5α-androstan-17a-one by PLC, as plates from ethyl acetate: mp 205–208 °C (lit.[7] 203–205 °C); IR 3600, 3440, 1700 cm^{-1}; NMR τ 9.21 (CH_3-19), 8.88 (CH_3-18), 6.00 (m, $W_{1/2}$ = 8 Hz, H-3).

Likewise with similar quantities **3b** was converted to 3.8 g of an oily mixture of **4b**, which was chromatographed on 300 g of silica gel. Chloroform–methanol (9:1) produced crude 17a-ketone, which on repeated recrystallization from ethyl acetate gave 3β,11α-dihydroxy-*D*-homo-5α-androstan-17a-one (**4b**) as needles: mp 233–235 °C; IR 3600, 3440, 1700 cm^{-1}; NMR τ 9.04 (CH_3-19), 8.87 (CH_3-18), 6.33 (m, $W_{1/2}$ = 22 Hz, H-3), 6.00 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1. Found: C, 75.3; H, 9.9.

***D*-Homo-5α-androstane-3,11-dione and 11α-Hydroxy-*D*-homo-5α-androstan-3-one.** A standard Huang–Minlon reduction of 1.2 g of **4b** gave 1.1 g of a yellow oil, homogeneous by TLC. A small portion, purified by PLC, gave *D*-homo-5α-androstane-3β,11α-diol as plates from hexane: mp 85–87 °C; IR 3600, 3420 cm^{-1}; NMR τ 9.17 (CH_3-18), 9.07 (CH_3-19), 6.34 (m, H-3) overlapped with 6.13 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.2. Found: C, 78.1; H, 11.0.

The crude diol (700 mg) was refluxed for 45 h with 10 g of silver carbonate on Celite[14] in 25 mL of benzene and sufficient chloroform to achieve steroid dissolution, the reaction being monitored by TLC. Filtration of insoluble material which was washed with ethyl acetate and evaporated gave an oil which was purified by PLC to give 660 mg of the title hydroxy ketone as needles from acetone: mp 134 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.13 (CH_3-19), 8.87 (CH_3-18), 6.07 (sx, J = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.1; H, 10.6.

The crude diol (300 mg) dissolved in acetone was treated with Jones reagent. Extraction gave 280 mg of the dione as a colorless chromatographically homogeneous oil, which defied attempts at recrystallization: IR 1700 cm^{-1}; NMR τ 9.19 (CH_3-18), 8.78 (CH_3-19); M^+ *m/e* 302. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.3; H, 10.1.

Similar treatment of the hydroxy ketone (500 mg) gave the dione (45 mg) having identical chromatographic behavior and NMR spectrum to that above.

Incubation of the Different Substrates with *Aspergillus ochraceus* Wilhelm (CBS 132.52).[15] General Procedure. A nutrient medium prepared from 2 g of malt extract, 2 g of beef extract, 2 g of yeast, 5 g of glucose, and 5 mL of cornsteep liquor dissolved in 1 L of distilled water and with pH adjusted to 5.5 with dilute hydrochloric acid was introduced into 1-L conical flasks in portions of 200 mL. After sterilization in an autoclave each flask was inoculated with 7 mL of a suspension of spores of the microorganism[13] prepared from slopes containing 2% nutrient agar and 3% malt extract under aseptic conditions, plugged with cotton wool, and agitated at room temperature (~25 °C) for 2 days. A solution of the steroid substrate in dimethyl sulfoxide was added under sterile conditions (80 mg of substrate in 12 mL of solvent per flask) and the flasks were shaken for the specified time. The contents of the flasks were combined and filtered through cotton wool. The mycelium was extracted with acetone in a Soxhlet and the aqueous portion after addition of sodium chloride was continuously extracted with ethyl acetate. The combined extracts were evaporated, leaving crude steroid mixtures.

The following substrates were subjected to this procedure.

***D*-Homoandrost-4-en-3-one** (380 mg) gave 240 mg of crude mixture. PLC separation yielded 30 mg of starting material, 55 mg of 6β,11α-dihydroxy-*D*-homoandrost-4-en-3-one recrystallized from ethyl acetate [mp 178–180 °C; IR 3600, 3440, 1670 cm^{-1}; NMR τ 9.08 (CH_3-18), 8.50 (CH_3-19), 6.00 (sx, *J* = 10, 10, 5 Hz, H-11), 5.60 (t, *J* = 3, 3 Hz, H-6), 4.20 (H-4); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.0; H, 9.6], and 74 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,6-dione as needles from ethyl acetate [mp 189–192 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.14 (CH_3-18), 8.94 (CH_3-19), 6.00 (m, $W_{1/2}$ = 20 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.4; H, 9.8.].

Oxidation of a small portion of the hydroxy dione with Jones reagent gave *D*-homo-5α-androstane-3,6,11-trione, which was recrystallized from ethyl acetate: mp 188–191 °C: IR 1710 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.84 (CH_3-19); M^+ *m/e* 316. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.9; H, 8.9.

***D*-Homo-5α-androstane-3,6-dione** (100 mg) gave 70 mg of crude material. PLC separation gave 50 mg of starting material and 15 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,6-dione. Both the hydroxy dione and the oxidation product were identical with those obtained in the preceding experiment.

***D*-Homo-5α-androstane-3,7-dione** (200 mg) gave 186 mg of crude material. Separation by PLC gave 48 mg of starting material and 32 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,7-dione as needles from acetone–hexane: mp 233–236 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.12 (CH_3-18), 8.60 (CH_3-19), 5.86 (m, $W_{1/2}$ = 19 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.4; H, 9.7.

Oxidation of 45 mg of the hydroxy dione with Jones reagent gave 40 mg of *D*-homo-5α-androstane-3,7,11-trione as a colorless oil which could not be crystallized: IR 1700 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.52 (CH_3-19). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.5; H, 8.8.

***D*-Homo-5α-androstane-3,17a-dione** (240 mg) gave a solid residue which was purified by PLC to give 185 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17a-dione recrystallized from ethyl acetate as needles: mp 202–207 °C; IR 3600, 1705 cm^{-1}; NMR τ 8.84 (CH_3-19 and CH_3-18), 6.07 (sx, *J* = 10, 10, 5 Hz, H-11); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.3; H, 9.5.

Oxidation of 40 mg of the hydroxy dione with Jones reagent yielded 35 mg of *D*-homo-5α-androstane-3,11,17a-trione, which was recrystallized from acetone–hexane: mp 230–233 °C (lit.[11] 226–228 °C); IR 1705 cm^{-1}; NMR τ 8.92 (CH_3-18), 8.73 (CH_3-19); M^+ *m/e* 316.

Standard Huang-Minlon reduction of 74 mg of hydroxy dione gave 60 mg of *D*-homo-5α-androstan-11α-ol from methanol: mp 121–124 °C; IR 3640 cm^{-1}; NMR τ 9.17 (CH_3-18), 9.06 (CH_3-19), 6.10 (sx, *J* = 10, 10, 5 Hz, H-11); M^+ *m/e* 290. Anal. Calcd for $C_{20}H_{34}O$: C, 87.5; H, 12.5. Found: C, 87.4; H, 12.8.

***D*-Homo-5α-androstane-3,17-dione** (85 mg) gave 80 mg of a pale yellow oil. Separation by PLC gave 10 mg of starting material and 54 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17-dione as needles from acetone: mp 207–210 °C; IR 3590, 1705 cm^{-1}; NMR τ 9.16 (CH_3-19), 8.85 (CH_3-18), 6.07 (sx, *J* = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.3; H, 9.7.

Oxidation of 35 mg of this hydroxy dione gave *D*-homo-5α-androstane-3,11,17-trione as a white solid, which was recrystallized from ethyl acetate: mp 229–231 °C; IR 1695 cm^{-1}; NMR τ 9.21 (CH_3-18), 8.74 (CH_3-19). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.1; H, 9.0.

A small portion of the hydroxy dione was acetylated with acetic anhydride–pyridine, forming 11α-acetoxy-*D*-homo-5α-androstane-3,17-dione as plates from ethyl acetate–acetone: mp 212–214 °C; IR 1705, 1250 cm^{-1}; NMR τ 9.10 (CH_3-18), 8.90 (CH_3-19), 8.00 ($OCOCH_3$), 4.87 (m, $W_{1/2}$ = 24 Hz, H-11). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.3; H, 9.0. Found: C, 73.1; H, 8.9.

***D*-Homo-5α-androstane-2,17a-dione** (300 mg) gave after purification by PLC 184 mg of starting material and 80 mg of 11α-hydroxy-*D*-homo-5α-androstane-2,17a-dione, which was recrystallized from acetone-hexane: mp 191–193 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.12 (CH_3-19), 8.90 (CH_3-18), 6.13 (sx, *J* = 10, 10, 5 Hz, H-11). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.2.

Oxidation of a small portion of the hydroxy dione gave *D*-homo-5α-androstane-2,11,17a-trione as a colorless oil: IR 1700 cm^{-1}; NMR τ 9.01 (CH_3-19), 8.98 (CH_3-18). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 75.7; H, 8.8.

3β-Hydroxy-*D*-homo-5α-androstan-17a-one (280 mg) gave 270 mg of crude material. Separation by PLC gave 105 mg of starting material, 75 mg of 11α-hydroxy-*D*-homo-5α-androstane-3,17a-dione identical with that obtained previously, and 85 mg of 3β,11α-dihydroxy-*D*-homo-5α-androstan-17a-one identical with that obtained by ring expansion of 3β,11α-dihydroxy-5α-androstan-17-one.

3α-Hydroxy-*D*-homo-5α-androstan-17a-one (75 mg) gave 65 mg of a crude mixture. Separation by PLC gave 50 mg of starting material and 25 mg of 3α,11α-dihydroxy-*D*-homo-5α-androstan-17a-one, which recrystallized from ethyl acetate as needles: mp 203–205 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.08 (CH_3-18), 8.91 (CH_3-19), 6.30 (m, $W_{1/2}$ = 20 Hz, H-11), 6.00 (m, $W_{1/2}$ = 8 Hz, H-3); M^+ *m/e* 320. Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.0; H, 10.1. Found: C, 74.7; H, 10.1.

A small portion of this dihydroxy ketone was oxidized in the usual manner, giving *D*-homo-5α-androstan-3,11,17a-trione identical with that described previously.

3β-Hydroxy-*D*-homoandrost-5-en-17a-one (235 mg) gave 200 mg of crude material. Separation by PLC gave 100 mg of starting material and 50 mg of 3β,11α-dihydroxy-*D*-homoandrost-5-en-17a-one as needles from ethyl acetate: mp 162–164 °C; IR 3600, 1700 cm^{-1}; NMR τ 8.83 (CH_3-18), 8.80 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 6.00 (m, $W_{1/2}$ = 22 Hz, H-11), 4.60 (q, *J* = 6, 2 Hz, H-6); M^+ *m/e* 318. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.4.

The product from several microbiological experiments (200 mg) was dissolved in 30 mL of diethylene glycol and the solution was refluxed for 1 h with 2 mL of hydrazine hydrate, before raising the temperature to 195 °C. After cooling the solution, 1 g of potassium hydroxide was added and the solution was heated for 3 h at 195 °C. After cooling and addition of water, the solution was acidified with concentrated hydrochloric acid, and extraction with benzene gave a spongy solid which was recrystallized from ethyl acetate to give 185 mg of *D*-homoandrost-5-ene-3β,11α-diol as needles: mp 84–86 °C; IR 3600 cm^{-1}; NMR τ 9.16 (CH_3-18), 8.86 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 6.00 (sx, *J* = 10, 10, 5 Hz, H-11), 4.60 (q, *J* = 6, 2 Hz, H-6). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.0; H, 10.5.

This diol (160 mg) was dissolved in acetone and treated with Jones reagent for 10 min. Dilution with water followed by ether extraction gave 120 mg of a yellow oil which was separated by PLC into 30 mg of *D*-homoandrost-4-ene-3,11-dione, which was recrystallized from ethyl acetate [mp 168–170 °C; IR 1700, 1670 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.56 (CH_3-19), 4.30 (H-4). Anal. Calcd for $C_{20}H_{28}O_2$: C, 80.0; H, 9.4. Found: C, 79.7; H, 9.3], and 20 mg of 3β-hydroxy-*D*-homoandrost-5-en-11-one as needles from ethyl acetate [mp 183–185 °C; IR 3600, 1700 cm^{-1}; NMR τ 9.21 (CH_3-18), 8.78 (CH_3-19), 6.40 (m, $W_{1/2}$ = 24 Hz, H-3), 4.60 (m, $W_{1/2}$ = 8 Hz, H-6). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.5; H, 9.9.].

The remaining three substrates were subjected to this incubation procedure on a similar scale to the other experiments described above. No hydroxylated products were detected and only starting material (see Table I) was recovered.

Registry No.—**1a**, 53-41-8; **1b**, 481-29-8; **2a**, 67010-38-2; **2b**, 67010-39-3; **3a**, 66966-84-5; **3b**, 52401-33-9; *D*-homo-5α-androstane-3β,11α-diol, 62193-45-7; *D*-homo-5α-androstane-3,6,11-trione, 62193-77-5; *D*-homo-5α-androstane-3,7,11-trione, 62193-82-2; *D*-homo-5α-androstane-3,11,17a-trione, 66966-85-6; *D*-homo-5α-androstan-11α-ol, 35649-44-6; *D*-homo-5α-androstane-3,11,17-trione, 62193-85-5; 11α-acetoxy-*D*-homo-5α-androstane-3,17-dione, 62193-69-5; *D*-homo-5α-androstane-2,11,17a-trione, 66966-86-7; *D*-homoandrost-5-ene-3β,11α-diol, 62193-46-8; *D*-homoandrost-4-ene-3,11-dione, 62193-55-9; 3β-hydroxy-D-homoandrost-5-en-11-one, 62193-41-3; trimethyloxosulfonium iodide, 1774-47-6; sodium azide, 26628-22-8; acetic anhydride, 108-24-7.

References and Notes

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Trianions from α-Hydroxy Carboxylic Acids

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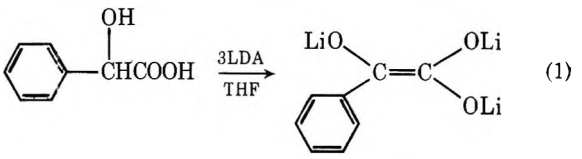
Polymetalated organic compounds are of both practical interest as synthetic reagents and of theoretical interest as models for charge distribution and stabilization.[1-3] The recent development and use of hindered amide bases has made many diverse types of mono- and dianions available by simple deprotonation reactions.[4-6] In this note, we wish to report the first preparation of a trianion from a substituted α-hydroxy acid (eq 1). The limitations of this procedure for forming such

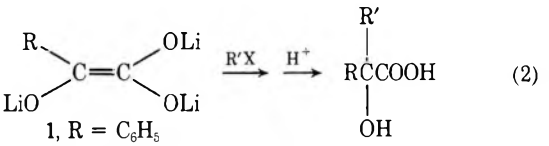


(1)

1

enetriolates have been evaluated and possible synthetic applications of these reactive intermediates have been explored. In addition, we have qualitatively compared the kinetic acidity of dilithio mandelic acid with other weak acids in an attempt to estimate the effect of an adjacent negatively charged electronegative atom on the acidity of a proton attached to the carbon.

Enetriolates like 1 are ambident nucleophiles which could react with electrophiles at either a nucleophilic carbon or oxygen. Based on the known reactions of alkoxyenediolates, geminal enediolates, or enamidolates,[4] alkylation at carbon to give a substituted α-hydroxy acid was expected. This was shown to be the case (see Table I) for enetriolate 1. However, alkylation of 1 or other enetriolates (eq 2) gives only modest



(2)

1, R = C_6H_5
2, R = CH_3
3, R = H

yields of product α-hydroxy acids and would not be synthetically useful when compared to existing procedures. Apparently deprotonation of alkyl halides by the enetriolates results in elimination reactions which compete with the desired substitution reaction. Efforts to increase the yield of desired alkylation product by addition of hexamethylphosphoramide (HMPA) failed, although a higher yield was obtained when an alkyl chloride was used instead of an alkyl bromide or iodide. Deprotonation of mandelic acid with *n*-BuLi (6 eq) and potassium *tert*-butoxide (3 eq) in pentane for 24 h at 25 °C followed by methylation with methyl iodide also failed to yield an alkylated product.[7]

Attempts to generate enetriolates **2** and **3** by deprotonation of glycolic and lactic acid were less successful as is noted in Table I. This failure could be ascribed to the expected de-

Table I. Products Formed in Reactions of Enetriolates with Various Electrophiles

α-hydroxy acid precursor	registry no.	electrophile	product	registry no.	% yield[a] product	% yield[a] (precursor)
mandelic acid	90-64-2	*n*-C_4H_9Cl	$C_6H_5C(n\text{-}C_4H_9)OHCO_2H$	4445-12-9	55	(8)
		n-C_4H_9Br			37	(56)
		n-C_4H_9Br[b]			18	(81)
		n-C_4H_9I			13	(71)
		c-$C_6H_{11}I$	none		0	
		D_2O	$C_6H_5CDOHCO_2H$	67315-76-8	58[c]	
		CH_3I	$C_6H_5C(CH_3)OHCO_2H$	515-30-0	40[d]	(60)
glycolic acid	79-14-1	*n*-$C_{10}H_{21}Br$	$(n\text{-}C_{10}H_{21})CHOHCO_2H$	2984-55-6	10[e]	
		n-$C_{10}H_{21}I$	[f]			
		CH_3I	$(CH_3)_2COHCO_2H$	594-61-6	~10[g]	
lactic acid	50-21-5	CH_3I	$(CH_3)_2COHCO_2H$		<10	

[a] Yields determined by GC after esterification (see text). [b] HMPA was added before the butyl bromide. [c] The crude acid before esterification was 41% d_1 by NMR. [d] The atrolactic acid yield was determined by NMR of the crude reaction mixture. [e] This is an isolated yield. [f] While no alkylation product was isolated, significant amounts of $C_{20}H_{42}$ from reductive dimerization of the *n*-$C_{10}H_{21}I$ were formed. [g] In addition, a trace of lactic acid was formed.

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crease in acidity of the dilithium derivatives of glycolic and lactic acids relative to that of mandelic acid. Alternatively, solubility problems in reactions leading to **2** and **3** may have interfered with the reactions.

The alkylation results imply at least a transitory existence for enetriolate **1**. Less ambiguous evidence for **1** includes the observation of 41% deuterium incorporation into mandelic acid when the reaction mixture was treated with 20% DCl in D_2O. Since low deuterium incorporation has been observed in deuterations of similar anions solvated by amines,[8] we believe that the alkylation results of **1** are best explained by assuming that nearly complete deprotonation of lithio mandelic acid to give **1** has occurred as shown in eq 1. This interpretation is also consistent with the results of the competition experiments discussed below.

We attempted to characterize enetriolate **1** by both UV–visible spectroscopy and ^{13}C NMR spectroscopy. In the UV–visible spectrum **1** exhibits only end absorption even in dilute solution (ca. 1×10^{-3} M). Absorption by other species in the base solution precluded measurement of either λ_{max} or an extinction coefficient. Solubility problems frustrated our attempts to measure the ^{13}C NMR spectrum of **1**.

We have qualitatively measured the kinetic pK_a of the dilithium derivative of mandelic acid using competitive deprotonation reactions. When a solution containing 1 equiv each of mandelic acid and phenylacetic acid was treated with 4 equiv of LDA, exclusive C–H deprotonation of the phenylacetic acid occurred as measured by the observation of deuterium incorporation only into the phenylacetic acid upon deuteration. Accordingly, we estimate that the kinetic pK_a of the dilithium derivative of mandelic acid is at least 2 units greater than that of the lithium salt of phenylacetic acid. In a similar experiment, an equal molar solution of mandelic acid and triphenylmethane was treated with 3 equiv of LDA under conditions which normally gave **1**. In this case deuteration with DCl in D_2O gave triphenylmethane which contained 5–15% deuterium at the methyl carbon; recovered mandelic acid again contained ca. 40% deuterium at C-2. Finally, treatment of an equal molar mixture of mandelic acid and decanoic acid with 4 equiv of LDA followed by a DCl/D_2O quench yielded a mixture of partially deuterated mandelic and decanoic acids. Thus, the α-C–H of the dilithium derivative of mandelic acid has kinetic acidity at least comparable (within 2 units) to triphenylmethane and lithium decanoate.

Unfortunately, the lack of thermodynamic pK_a values for lithium salts of carboxylic acids precludes us from making a quantitative statement concerning the effect of an adjacent negatively charged heteroatom on C–H pK_a. Qualitatively the α-O–Li group has, as expected, lowered the kinetic acidity of this proton and the α-O–Li has an effect comparable to that of a phenyl substituent[9] but in the opposite direction.

Experimental Section

All preparations involving active organometallic compounds were conducted under nitrogen using conventional inert atmosphere techniques. NMR spectra were recorded on a Varian T-60 NMR spectrometer. Analytical gas chromatography was performed on a 6 ft × ⅛ in. SE-30 column using a Hewlett Packard Model 3830 gas chromatograph. Cyclohexyl iodide was prepared by the method of Stone and Shechter.[10] All other reagents were purchased from commercial sources in reagent quality and used without further purification. Alkylation products were converted to ethyl esters and identified by NMR spectral and gas chromatographic comparison to authentic materials. THF was distilled from sodium–benzophenone, and HMPA was distilled at reduced pressure from sodium. Deuterium incorporation was determined by comparing the integrals of various peaks in the NMR spectra of the deuterated compounds.

General Procedure. A solution of ca. 1 mmol of α-hydroxy acid and an equivalent amount of internal standard in 10 mL of THF was added at −78 °C to a THF solution containing 3.3 equiv of LDA (from diisopropylamine and *n*-BuLi). The resulting mixture was allowed to warm and was stirred for 1 h at 25 °C and then cooled to −78 °C. A THF solution of 2 equiv of the electrophile was added and the mixture was allowed to warm and was stirred at 25 °C for 24 h. Following conventional acidic workup, the product was extracted into ether and the ethereal solution was distilled in vacuo. The residue was esterified in ethanolic HCl and the esterified products were analyzed by gas chromatography.

Deuterations. After preparation of the enetriolate as described above, the reaction mixture was added by syringe to an excess of 20% DCl in D_2O and then worked up immediately and analyzed by NMR for deuterium incorporation.

Acknowledgments. This work was generously supported by the Robert A. Welch Foundation.

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Synthesis of *tert*-Butoxymethyl Ethers: A New Protecting Group for Alcohols

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A common protecting group for alcohols and phenols is the methoxymethyl ether (I), available in high yield from ei-

$$ROCH_2OCH_3$$

I

ther chloromethyl methyl ether[1] or dimethoxymethane.[2] Unfortunately, removal of this protecting group often requires conditions too vigorous for sensitive functionalities (hot aqueous mineral acid).[1-3] Because of the relative lability of the *tert*-butyl protecting group,[4] we reasoned that the corresponding *tert*-butoxymethyl ether (II) would decompose

$$ROCH_2OC(CH_3)_3$$

II

readily under mild conditions and thus extend the utility of acetals as an alcohol protecting group.[5] Consequently, we set out to prepare chloromethyl *tert*-butyl ether, a hitherto unknown compound.

This task proved to be more difficult than had been anticipated. The reaction of an alcohol with formaldehyde or trioxane and hydrogen chloride gives the corresponding chloromethyl ether[6] but all attempts to generate the desired compound in this way failed. The reaction of *tert*-butyl alcohol with paraformaldehyde or trioxane in the presence of aqueous or gaseous hydrogen chloride or hydrogen bromide

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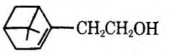
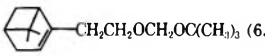
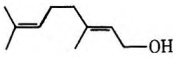
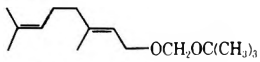
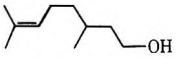
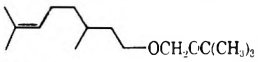
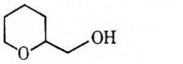
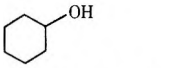
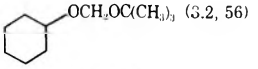
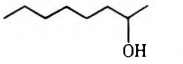
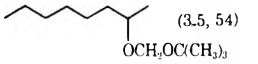
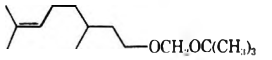
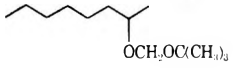
Table I. Conversion of Alcohols into *tert*-Butoxymethyl Ethers

alcohol	registry no.	acetal (g, %)[a]	registry no.
$CH_3(CH_2)_5OH$	111-27-3	$CH_3(CH_2)_5OCH_2OC(CH_3)_3$ (8.8, 79)	66922-41-6
$CH_3(CH_2)_7OH$	111-87-5	$CH_3(CH_2)_7OCH_2OC(CH_3)_3$ (4.6, 71)	66922-42-7
$C_6H_5CH_2OH$	100-51-6	$C_6H_5CH_2OCH_2OC(CH_3)_3$ (8.7, 76)	66922-43-8
	128-50-7	 (6.6, 80)	66922-44-9
	624-15-7	 (5.0, 70)	66922-45-0
	106-22-9	 (5.4, 74)	66922-46-1
	100-72-1	 (3.6, 60)	66922-47-2
	108-93-0	 (3.2, 56)	66922-48-3
	123-96-6	 (3.5, 54)	66922-49-4

[a] Refers to pure, isolated product.

Table II. Deprotection of *Tert*-Butoxymethyl Ethers

acetal	% yield of alcohol[a]
$CH_3(CH_2)_7OCH_2OC(CH_3)_3$	85
	88
	86
	90

[a] Refers to pure, isolated product.

yields the corresponding *tert*-butyl halide as the only product.

The other method which was examined as a possible route to the desired chloro ether is the free radical halogenation of *tert*-butyl methyl ether.[7,8] Unfortunately, *N*-bromosuccinimide[8] gives only *tert*-butyl bromide when reacted with *tert*-butyl methyl ether and sulfuryl chloride[8,9] did not react. On the other hand, chlorine[8] and *N*-chlorosuccinimide (NCS)[8] each produce the desired chloro ether. Because of the relative inconvenience of using chlorine, NCS is the reagent of choice. Thus, *tert*-butyl methyl ether and NCS yield chloromethyl *tert*-butyl ether as a solution in CCl_4 which is stable under nitrogen at room temperature.[10]

With the chloro ether in hand, synthesis of the acetals is easy. The alcohol is dissolved in THF and stirred with the chloro compound in the presence of triethylamine. Table I shows the alcohols which have been protected in this way. For example, 1-hexanol gives the corresponding *tert*-butoxymethyl acetal in 79% isolated yield. Phenols do not work as well; phenol (2.82 g) yields 1.37 g (25%) of *tert*-butoxymethyl phenyl ether and *m*-methoxyphenol gives 23% of the corresponding acetal. On the other hand, *tert*-butoxymethyl phenyl sulfide is isolated in 82% yield from thiophenol.

Deprotection of the acetals II is accomplished with aqueous trifluoroacetic acid at room temperature (see Table II). For example, citronellol is obtained in 86% yield, showing that no side reaction occurred during deprotection despite the presence of a nucleophilic double bond. Under identical conditions, the methoxymethyl ether of 1-octanol is stable so that the goal of designing an acetal protecting group which is more labile than methoxymethyl ethers is attained. It is of interest that the *tert*-butoxymethyl ethers are stable to hot glacial acetic acid, aqueous acetic acid at room temperature, and anhydrous trifluoroacetic acid at room temperature. Consequently, other acid-sensitive protecting groups can be removed selectively.

Application of this new protecting group in the selective manipulation of polyfunctional molecules is under investigation.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 nuclear magnetic resonance spectrometer and a Perkin-Elmer Model 237B grating spectrometer was used for infrared spectra.

A general experimental procedure follows.

Methyl *tert*-butyl ether[11] (100 mmol) is dissolved in 70 mL of CCl_4 and stirred with 120 mmol of NCS for 6 h with Hanovia sun lamp irradiation. The reaction flask is placed in a water bath and maintained at 35–38 °C[12] during the irradiation. The succinimide is removed by filtration and NMR analysis of the filtrate shows the chloromethyl *tert*-butyl ether (δ 1.25 (s, 9 H), 5.60 (s, 2 H)).

The alcohol (30 mmol) is dissolved in 20 mL of THF and stirred with triethylamine (120 mmol). This solution is cooled to −20 °C (dry ice/CCl_4) and the chloro ether solution from above (precooled to −20 °C) is added. The reaction mixture is allowed to warm to room temperature, stirred for 3 h, and filtered. The brown solution is separated, dried, and concentrated. Chromatography of the crude product through alumina with hexane removes a nonpolar by-product. Continued elution with benzene yields the *tert*-butoxymethyl ether which is then distilled.[13]

The acetal (4.2 mmol) is mixed with 19 mL of 1:1 trifluoroacetic acid–water and enough THF is added to make the reaction mixture homogeneous. After 48 h, workup with aqueous $NaHCO_3$ yields the crude alcohol which is purified by Kugelrohr distillation. The pure alcohol is identical with authentic material by IR, NMR, and TLC.

Registry No.—*tert*-Butyl methyl ether, 1634-04-4; chloromethyl *tert*-butyl ether, 40556-01-2.

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(6) See, for example, (a) the synthesis of chloromethyl methyl ether: C. S. Marvel and P. K. Porter, "Organic Synthesis", Collect. Vol. I, 2nd ed, A. H. Blatt, Ed., Wiley, New York, N.Y., 1941, p 377; (b) the preparation of methoxyethyl chloromethyl ether: E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976); and (c) a review on α-halo ethers: L. Summers, *Chem. Rev.*, **55**, 301 (1955).
(7) Ethers are halogenated on the α carbon: M. L. Poutsma in "Methods in Free Radical Chemistry", Vol. 1, E. S. Huyser, Ed., Marcel Dekker, New York, N.Y., 1969, p 137.
(8) Methods for the free-radical halogenation of organic compounds have been reviewed: E. S. Huyser, *Synthesis*, 7 (1970).
(9) Sulfuryl chloride has been used to chlorinate tetrahydrofuran (THF): C. G. Kruse, N. L. J. M. Broekhof, and A. van der Gen, *Tetrahedron Lett.*, 1725 (1976).
(10) All attempts to isolate the chloro ether by concentration have led to decomposition.
(11) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, 54, 2088 (1932).
(12) There is no reaction at 0 °C after 4 h but a satisfactory reaction rate is obtained at room temperature. The water bath is used for cooling purposes only.
(13) The ^{1}H NMR spectra of the *tert*-butoxymethyl ethers show singlets at δ 4.1–4.7 (2 H) and 1.2–1.25 (9 H). The corresponding ^{13}C NMR spectra are also consistent with the proposed structures. For example, the acetal and quaternary carbons are found at δ 89.248 and 74.251, respectively, for the benzyl alcohol acetal and δ 90.038 and 74.068, respectively, for the 1-hexanol acetal.

Desiccant Efficiency in Solvent Drying. 3. Dipolar Aprotic Solvents[1,2]

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It is generally acknowledged that dipolar aprotic solvents are the media of choice in some reactions and are unique in facilitating others.[3] The special solvent effects of molecules such as DMF and Me_2SO are attributable to their large dielectric constants coupled with the absence of solvation by hydrogen bonding and typically manifest themselves in properties such as poor anion solvation, voracious cation solvation, and a marked hydrophilicity. For the chemist, this latter feature is unfortunate since small amounts of water in these systems can diminish[3,4] their nucleophilicity and may even be hazardous to some operations.[5] The drying of these solvents is thus of paramount importance, but in these cases, as previously,[1] the chemical literature contains little reliable quantitative data.

We have recently developed a method of solvent water assay which utilizes a tritiated water tracer for the determination of water content.[6] The method circumvents many of the problems encountered in other assay methods and has provided some new correlations on the efficiency of desiccants.[1,2] For example, it has been shown that, rather surprisingly, the efficiency of a given desiccant is strongly dependent upon the solvent type,[1] and there is thus much uncertainty in extrapolating generalizations from one solvent type to another.

The method has now been applied to the desiccation of the dipolar aprotics acetone, DMF, Me_2SO, and HMPT. Since the dielectric constants of these solvents range between 20.7 (acetone) and 46.7 (Me_2SO), their rigorous desiccation is expected to be difficult.

Results and Discussion

Drying of Hexamethylphosphoric Triamide (HMPT). *Caution! HMPT is a suspected carcinogen.* Although in recent years the favored desiccant for HMPT appeared to be calcium hydride,[7] drying has also been previously accomplished with alkali metals,[5,8] alkali metal earth oxides,[8] and 4A[9a] and 13X[9b] molecular sieves.

The results with the siccatives summarized in Table I are largely self-evident, but the following points are worth noting. The extreme resistance to desiccation is demonstrated by the impossibility of obtaining *super-dry*[10] HMPT under any of the conditions used here. Even sequential drying,[11] which was previously found to be effective with acetonitrile,[2] falls short in this case. The use of sodium–potassium alloy as a drying agent seems questionable in view of the thermal instability of solutions of alkali metals in solvents of this type.[12]

Since phosphorus pentoxide causes loss of material through side reactions, the best procedure for drying HMPT appears to be distillation from calcium hydride followed by storage over molecular sieves.

Drying of Dimethylformamide One source[8] observes that it is doubtful whether distillation alone can remove water from this solvent and recommends a chemical method for the elimination of protonic impurities. 4A molecular sieves, alumina, potassium hydroxide, and calcium hydride have all been endorsed as siccatives[8] for DMF.

The results in Table II indicate the powerful hydrophilicity of this solvent, although sequential drying with 3A sieves almost achieves *super-dryness*. Interestingly, and contrary to an earlier suggestion,[13] while some of the basic dessiccants investigated are totally inept, e.g., alumina and potassium carbonate, others such as calcium hydride and potassium hydroxide achieve quite reasonable drying levels. Also, although seldom advocated for use in this circumstance, phosphorus pentoxide is a commendable desiccant. For DMF, however, barring impurities other than water, by far the

Table I. Efficiency of Desiccants in the Drying[a] of HMPT[b]

desiccant	residual solvent water content, ppm				
	6 h	24 h	72 h	144 h	other conditions
P_2O_5	1840[c]				22[d]
CaH_2	1750	857	347	248	80[d]
B_2O_3					190[e]
3A molecular sieves	1380	595	307	239	
4A molecular sieves	1167	610	344	269	29[f]
KOH (powdered)	1380	840	404		321[f]
Na–K					1620[d,g]
BaO	2190	1540	1040		
CaO	2360	2034	1890	1380	
$CaSO_4$	2080				
Al_2O_3	2134				

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2620 ppm (0.262% w/w). [c] Strongly colored solution. [d] Distilled sample. [e] Stirring for 24 h followed by distillation. [f] Sequentially dried sample, 72 h. [g] Significant quantities of dimethylamine are released on distillation.

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Table II. Efficiency of Desiccants in the Drying[a] of DMF[b]

desiccant	residual solvent water content, ppm 6 h	24 h	72 h	other conditions
3A molecular sieves	500	167	98	1.5[c]
P_2O_5	879	105		2[d]
CaH_2	641	227	102	94[d]
4A molecular sieves	454	134	108	
KOH (powdered)	1360	1110		303[d]
B_2O_3				890[e]
BaO	2060	1520	1140	
CaO	2090			
Al_2O_3	1970			
$CaSO_4$	2310	2030	1420	
K_2CO_3	2500			

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2860 ppm (0.286% w/w). [c] Sequentially dried sample, 72 h. [d] Distilled Sample. [e] Stirring for 24 h followed by distillation.

simplest and most effective method is sequential drying with 3A molecular sieves.

Drying of Dimethyl Sulfoxide (Me_2SO). Although calcium hydride[14a] and molecular sieves[14b] appear to be approved desiccants, the drying of Me_2SO has also been accomplished with a large variety of other siccatives.[8] Calcium sulfate, alkali earth metal oxides, alkali metal hydroxides, alumina, and, surprisingly perhaps, fractional distillation alone[15] have all been utilized.

Perhaps the most unexpected result (Table III) is that fractional distillation, discarding the first 20% of the distillate, affords desiccation of similar magnitude to that obtained with molecular sieves! This result is most surprising in view of the high dielectric constant and hygroscopicity of Me_2SO.

The interpretation of other results for Me_2SO is not so straightforward. For many of the basic desiccants, e.g., calcium hydride and calcium and barium oxides, initial dehydration is followed by an increase in *apparent* water content, and this indicates a base-catalyzed exchange between the acidic α protons of Me_2SO and labeled water. This suggestion is supported by a desiccation experiment with powdered potassium hydroxide which gave very little *apparent* drying. In this case, standing for 2 or 3 h over the desiccant produced yellow solutions, most likely indicating the presence of the dimsyl ion, which would of course lead to labeled solvent through exchange processes.

Although the results with the basic desiccants are therefore not very conclusive, a necessary corollary in the case of calcium hydride is, however, that drying is relatively slow, and perhaps not very efficient. A similar result for this desiccant was noted earlier with acetonitrile.[1]

In summary, although phosphorus pentoxide gave the best drying, it also induced significant decomposition, and the method of choice for Me_2SO would appear to be initial fractional distillation followed by sequential drying with molecular sieves.

Drying of Acetone. Acetone has been dried with a wide spectrum of desiccants.[8] Thus, alumina, calcium chloride, phosphorus pentoxide, and 4A molecular sieves,[16] as well as calcium and (anhydrous) cupric sulfate, have all been used.

Since acetone has the lowest dielectric constant of the solvents investigated here, it might be predicted that its drying should be relatively easy. In fact, in many respects the drying of acetone proved to be the most difficult case. As with Me_2SO, the root of the difficulty is the acidic α protons, which in this case compounds the drying problem not only by inflating *apparent* water content by exchange process but also by providing a pathway to self-condensation through enol intermediates. This facet of acetone chemistry makes the choice of a successful desiccant a delicate process. As Table IV shows, mild siccatives such as calcium sulfate are inept; more potent desiccants such as molecular sieves exhibit a short initial drying action but thereafter actually cause disastrous *increases* in water content by displacement of the condensation equilibrium. This interpretation was confirmed for molecular sieves and other basic desiccants such as barium oxide by gas chromatographic analysis which demonstrated the presence of mesityl oxide in the dried solvent (see Table IV).

In summary, while both cupric sulfate and 3A molecular sieves are clearly at least useful preliminary desiccants, the agent *par excellence* for acetone is powdered boric anhydride. Using stirring and sequential drying conditions, this siccati gave a solvent containing only 18 ppm of water and caused detectable condensation. In fact, the true water content likely to be lower as even with the premise that drying occ considerably faster than other processes, some labeling via t enol surely occurs on preparation of the standard wet sol tion.

In view of the remarkable efficiency of this desiccant acetone and acetonitrile,[1] it is puzzling that boric anhydri is not particularly outstanding for other members of this ser (Tables I–III). This finding emphasizes once more the danger in assuming the existence of any kind of absolute scale in the efficiency of desiccants for solvent drying.

Table III. Efficiency of Desiccants in the Drying[a] of Me_2SO[b]

desiccant	residual solvent water content, ppm 6 h	24 h	72 h	144 h	other conditions
4A molecular sieves	978	471	332	318	10[c]
3A molecular sieves	1050	448	269	226	
none					261[d]
P_2O_5					1.4[e,f]
B_2O_3					897[g]
CaH_2	1560		1820	1740	1802[e]
BaO	1450	1330	1770	2251	
CaO	2060		1740	1800	
Al_2O_3	1840	1900	1920		
K_2CO_3	2280	2200			
KOH (powdered)	2130[h]				2190[e]
$CaSO_4$	2140				

[a] Static drying modes unless otherwise specified. [b] Desiccant loading 5% w/v; initial water content 2560 ppm (0.256% w/w). [c] Sequentially dried sample, 72 h. [d] Fractionally distilled sample. [e] Distilled sample. [f] Contaminated by decomposition products. [g] Stirring for 24 h followed by distillation. [h] Yellow colored solutions.

Table IV. Efficiency of Desiccants in the Drying[a] of Acetone[b]

desiccant	residual solvent water content, ppm 6 h	24 h	72 h	other conditions
B_2O_3				18[c,d]
				47[c,e]
				107[f]
3A molecular sieves	115	152	322[g]	322[h]
$CuSO_4$ (anhydrous)	1920	972	579	1700[h]
4A molecular sieves	331	887	1720	
$CaSO_4$	1590	1600		
BaO	1910	1870[i]		
P_2O_5	*j*			1970[f]
K_2CO_3	2057	2250		

[a] Static drying modes unless specified otherwise. [b] Desiccant loading 5% w/v; initial water content 2710 ppm (0.271% w/w), unless specified otherwise. [c] Initial water content 2890 ppm (0.289% w/w). [d] Stirred, distilled, and sequentially dried, 24 h. [e] Stirred for 24 h and distilled. [f] Dried for 24 h and then distilled. [g] Contamination (2%) by mesityl oxide. [h] Fractionated sample. [i] Contamination (12%) by mesityl oxide. [j] Brown-black solutions.

Experimental Section

Desiccants. Details of the source, activation, and handling of most of the desiccants have already been described.[1] Reagent grade cupric sulfate was activated by heating at 320 °C for 15 h before use. Barium and calcium oxides were of reagent grade, and a fresh batch was used directly without activation.

Solvents. DMF, Me_2SO, and HMPT were commercial synthetic grades of 99% purity (Merck). Acetone was of analytical grade (M&B). All solvents were rigorously purified by standard methods.[8]

HMPT and Me_2SO were treated by standing over barium oxide overnight, followed by filtration, distillation from calcium hydride, and subsequent storage over 20% w/v 4A molecular sieves. Me_2SO had bp 74.5–75.0 °C at 12 mmHg, and HMPT had bp 89.0–89.5 °C at ~3 mmHg.

Commercial DMF was allowed to stand over 4A molecular sieves overnight and was filtered, distilled from phosphorus pentoxide (bp 55.8–56.0 °C at 20 mmHg), allowed to stand over anhydrous potassium carbonate, and subsequently stored over 4A molecular sieves.

Analytical grade acetone was allowed to stand over anhydrous potassium carbonate for one day and then over 4A molecular sieves overnight. Fractionation gave material, bp 56.2 °C, which was not stored but used immediately. Gas chromatographic analysis of this material showed it to be free of impurities.

Techniques. The procedure used for HMPT serves as an example. A stock solution of HMPT containing 2620 ppm of labeled water was prepared by the addition of 0.50 g of tritiated water, specific activity 0.5 mCi/mL, to the appropriate mass of purified rigorously dried HMPT. Aliquots of the stock solution (15.0 ± 0.1 mL) were syringed directly onto the appropriate desiccant contained in a 25 mL clear-fit round-bottom flask, which was immediately stoppered. Experiments were conducted at ambient temperatures (26–30 °C). Where specified, samples were stirred magnetically. Aliquots (1.00 ± 0.02 mL) were taken at time intervals as specified in Table I and assayed directly by liquid scintillation counting, as previously described.[1,2] Where necessary, viz., in the case of colored solutions or suspected contamination by soluble desiccant residues, samples were distilled before assay. Sequential drying[2] was accomplished by decanting *monosiccated* solvent onto a fresh charge of 5% w/v desiccant. Sampling was then effected at the time intervals given in the table footnotes.

Registry No.—HMPT, 680-31-9; DMF, 68-12-2; Me_2SO, 67-68-5; acetone, 67-64-1.

References and Notes

(1) Part I: D. R. Burfield, K. H. Lee, and R. H. Smithers, *J. Org. Chem.*, **42**, 3060 (1977).
(2) For Part 2, see D. R. Burfield, G. H. Gan, and R. H. Smithers, *J. Appl. Chem. Biotechnol.*, **28**, 23 (1978).
(3) See, for example, Heinz Becker et al., "Organicum, Practical Handbook of Organic Chemistry", translated by B. J. Hazzard, Pergamon Press, Braunschweig, 1973, pp 185, 190. See also L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–5, Wiley, New York, N.Y., 1967, 1969, 1972, 1974 and 1975.
(4) For an interesting recent study involving Me_2SO–H_2O mixtures, see L. F. Blackwell and J. L. Woodhead, *J. Chem. Soc., Perkin Trans. 2*, 1218 (1975).
(5) The reaction of sodium hydride with Me_2SO has been reported to sometimes give rise to violent explosions; inter alia, see L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971, p 24. However, in our hands, the same reaction has been carried out a number of times using stringently dried solvent with no untoward effects. While the cause of these accidents remains undetermined, it is noteworthy that the equilibrium water content of Me_2SO is 10%, and it thus seems not unlikely that the origin of these mishaps may lie in the use of insufficiently dried solvents.
(6) D. R. Burfield, *Anal. Chem.*, **48**, 2285 (1976).
(7) See, for example, B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977).
(8) See references contained in J. A. Riddick and W. B. Bunger, "Organic Solvents", 3rd ed., Wiley-Interscience, New York, N.Y., 1970.
(9) (a) F. Trondlin and C. Rüchardt, *Chem. Ber.*, **110**, 2949 (1977); (b) T. J. Wallace and A. Schriesheim, *Tetrahedron*, **21**, 2271 (1965).
(10) Here, as earlier,[1,2] the term *super-dry* denotes solvents containing less than 1 ppm of water.
(11) See Experimental Section.
(12) C. A. Young and R. R. Dewald, *J. Chem. Soc., Chem. Commun.*, 188 (1977).
(13) See S. S. Pizey, "Synthetic Reagents", Vol. 1, Ellis Horwood Ltd., Chichester, 1974. This author reports that the use of calcium hydride and other basic desiccants in the drying of DMF could produce significant amounts of dimethylamine. However, the presence of this amine would give rise to inflated *apparent* water contents, and the values observed here, both for statically dried and distilled samples, suggest that this side reaction is of minor importance for these desiccants.
(14) (a) D. Martin and H. G. Hauthal, "Dimethyl Sulphoxide", translated by E. S. Halberstadt, Wiley-Halsted, New York, N.Y., 1975. (b) H. E. Baumgarten, Ed., "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, pp 243, 756.
(15) W. H. Smyrl and C. W. Tobias, *J. Electrochem. Soc.*, **115**, 33 (1968).
(16) R. L. Meeker, F. Critchfield, and E. T. Bishop, *Anal. Chem.*, **34**, 1510 (1962).

3,4-Dimethyl-*cis*-bicyclo[3.3.0]-3-octene-2,8-dione: A Potentially Useful Pentalenolactone Synthon

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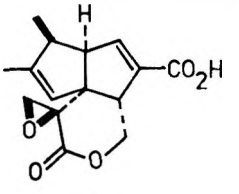
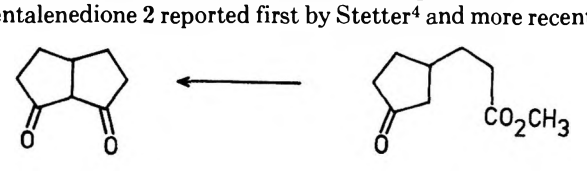
Pentalenolactone (**1**) is an acidic lipophylic antibiotic isolated from the fermentation broth of *Streptomyces* UC 5319



1

which exhibits inhibitory activity against nucleic acid synthesis in bacterial cells.[1,2] Both the novel structural nature of pentalenolactone together with its biological activity prompted us to consider possible routes to the synthesis of this molecule.

Inspection of the literature revealed a number of potential pentalene synthons,[3] the most interesting of which was the pentalenedione **2** reported first by Stetter[4] and more recently



2 **3**

by Eaton.[5] The salient feature of both the Stetter and Eaton routes was the base-induced internal Claisen condensation of the ester **3**, which in Eaton's hands gave an excellent yield of the dione **2**. These data inspired us to consider the possi-

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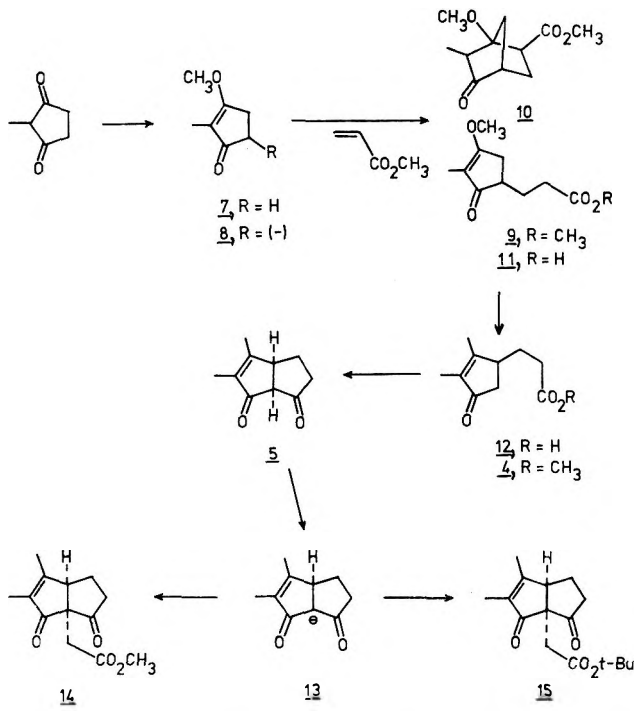
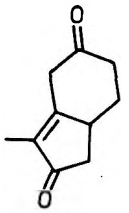


bility of carrying out a base-promoted cyclization of the cyclopentenone ester **4** in the hope that it would lead to the pentalenedione **5**. No analogous intramolecular Claisen cyclization examples were found that suggested base treatment of **4** would lead to formation of a new cyclopentanone ring (compound **5**) in preference to formation of a new cyclohexanone ring (compound **6**), and therefore we set out to resolve this question by experiment.



6

The synthesis of compound **4** has its origin in a body of data, mostly unpublished, which centers around the aprotic and low temperature conjugate addition reaction of several different enolate species with electron deficient olefins.[6] Within the context of the preparation of **4**, it occurred to us that the vinylogous ester **7** might serve as a starting point since Stork and Danheiser have shown that kinetic deprotonation of vinylogous esters derived from six-membered ring β-diketones takes place at the α'-carbon atom and not at the γ-carbon atom.[7] Several reactions of these enolate systems with electrophiles, excepting electron deficient olefins, have been observed.[7] On the assumption that **7** would form the enolate **8**, we were interested in examining the possible conjugate addition of this anion to methyl acrylate. Lee has reported that kinetic enolates derived from cyclohexenones react with acrylate esters to afford bicyclo[2.2.1]heptanone derivatives with no trace of the monocyclic Michael adducts observed.[8] We felt, however, that it might be possible to control the reaction of enolate **8** with methyl acrylate by judicious regulation of temperature and so obtain formation of the monocyclic adduct **9** in preference to the bicyclic adduct **10**. Indeed, this artifice has proven experimentally tenable using the following reaction sequence.

Treatment of 2-methylcyclopentane-1,3-dione[9] with methanol, trimethyl orthoformate, and a small amount of sulfuric acid gave the crystalline vinylogous methyl ester **7**. Kinetic deprotonation of **7** at −78 °C with 1 equiv of lithium diisopropylamide gave the enolate **8**,[10] which was then reacted with methyl acrylate to give in excellent yield a mixture of the adducts **9** and **10** in a ratio of 82:18, respectively. The question of how to deal with this mixture of adducts was answered when the esters were submitted to base hydrolysis using potassium hydroxide in water/methanol, first at 0 °C and then at room temperature. Isolation of the acidic fraction from this reaction gave a single crystalline acid identified as **11**.[11]

The conversion of **11** into the cyclopentenone ester **4** was initiated by reaction with methyllithium at −78 °C for 14 h. This reaction gave a 92% yield of a mixture of materials consisting of compounds **11** and **12** in a 1:4 ratio, respectively.[12] Methylation of this mixture with diazomethane followed by chromatography results in clean separation of the esters **4** and **9**. The overall yield for the conversion of **11** into **4** is 70% based on recovered and reused ester **9**.

Intramolecular Claisen condensation of **4** using the conditions described by Eaton (sodium methoxide in ether at room temperature) failed to give any reaction.[5] However, when benzene was substituted for ether as the solvent, rapid cyclization of **4** (10 min) occurred, providing that the reaction was carried out in a distillation apparatus at 120 °C (pot temperature) to ensure the removal of methanol. Inverse quenching of the reaction mixture with potassium dihydrogen phosphate[13] followed by standard workup gave a yellow solid which consisted of the diketone **5** together with several minor components. Sublimation of this material gave pure white crystals of **5** in 70% yield. In agreement with Eaton's findings,[5] the diketone showed little tendency to exist in the enolized form, a phenomenon that gives rise to relatively simple IR and NMR spectra for the compound. Interestingly, no evidence for the presence of the diketone **6** could be detected under a variety of cyclization conditions.[14]

Of potential importance to our intended synthesis of pentalenolactone was the viability of carbon alkylation of the β-diketone enolate derived from **5**. A sodium enolate of **5** must be the initial reaction product arising from cyclization of **4**. The same type of enolate must also result from the cyclization of **3** into **2**.[5] No reactions stemming from pentalene diketone enolates of this type have been reported, however. Although we have not attempted to alkylate the sodium enolate of **5** as it is formed from **4**, we have successfully alkylated its potassium enolate (**13**), which on reaction with either methyl iodoacetate or *tert*-butyl iodoacetate affords the corresponding ester diketones **14** and **15** in excellent yields.

Further work with the diketone **5** pursuant to the total synthesis of pentalenolactone is in progress.

Experimental Section

General Section. Nuclear magnetic resonance (NMR) spectra were recorded at 100 MHz on a Jeolco Model JNM-MH-100 high-resolution spectrometer. Samples were examined in deuteriochloroform containing 1% by volume of tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrophotometer. Samples were analyzed in spectrograde chloroform solutions of 0.1 mm thickness. Mass spectra were obtained on a Dupont Model 21-940 B mass spectrometer.

Chromatography was performed as follows. The silica, #7731 gel G type 60 for TLC, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under water aspirator vacuum, and the silica was repressed to avoid channeling between the glass and the silica. The compound was deposited with a minimal amount of solvent and then eluted with solvent using the water aspirator as a vacuum source.

Preparation of the Vinylogous Ester 7. To a solution of 2-methylcyclopentane-1,3-dione (20.0 g, 0.1786 M), trimethyl orthoformate (117 mL), and methanol (350 mL) was added concentrated sulfuric acid (9.9 mL). The resulting mixture was refluxed for 2 h, whereupon the majority of the methanol was removed under vacuum. Saturated $NaHCO_3$ was added until the mixture was pH 8. Extraction with $CHCl_3$ followed by filtration of the extracts through $MgSO_4$ and

evaporation to dryness resulted in a yellow solid which on sublimation at 70 °C (10^{-3} mm) gave white crystals of **7** (21.3 g, 95%): mp 59.5–60 °C; R_f (silica) (5% CH_3OH in $CHCl_3$) 0.56, (ether) 0.26; IR ν_{max} 1690 (w, C=O), 1630 (s, C=C—OCH_3) cm^{-1}; NMR δ 1.6 (s, 3 H), 2.2 (m, 2 H), 2.65 (m, 2 H), 4.00 (s, 3 H); MS *m/e* 126 (100), 111 (25), 96 (62), 95 (32), 83 (45).

Preparation of the Acid 11. To a 1 M THF solution of lithium diisopropylamide [84.5 mmol; prepared from 11.83 mL of diisopropylamine and 34.9 mL of *n*-butyllithium (2.42 M)] was added **7** (10.642 g, 84.5 mmol, 1 M in THF) at such a rate as to keep the internal temperature of the reaction below −67 °C. After addition was complete, the mixture was stirred for 20 min, whereupon methyl acrylate (84.5 mmol, neat) was added sufficiently slowly to keep the internal temperature of the reaction below −65 °C. The resulting mixture was stirred for 2 h at −78 °C and then quenched at −78 °C with 18 mL of 6 N HCl followed by 10 mL of water. Extraction with ether (3 × 100 mL) and drying the combined extracts first over $NaSO_4$ and then by filtration through $MgSO_4$ followed by evaporation gave 16.85 g of an oil (94% crude yield) consisting of a 82:18 mixture (NMR analysis) of the esters **9** and **10**, respectively.

A portion of this mixture (7.626 g, 36 mmol) dissolved in methanol (36 mL) was treated with 2.37 g of 85% KOH in water (36 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h, followed by extraction with ether (100 mL). Acidification of the aqueous phase to pH 3 with 6 N HCl, extraction with CH_2Cl_2, and drying first over Na_2SO_4 and then by filtration through $MgSO_4$ followed by evaporation of the solvent gave 6.6 g of **11** (mp 105–110 °C; 92.5% yield). Two recrystallizations from ether/$CHCl_3$ gave **11**: mp 119–120 °C; IR ν_{max} 1735–1690 (broad, CO_2H and C=O), 1630 (s, C=C—OCH_3) cm^{-1}; NMR δ 1.6 (s, 3 H), 1.6–3.0 (m, 7 H), 3.95 (s, 3 H); MS *m/e* 198 (34), 153 (12), 139 (68), 126 (100).

Preparation of Ester 4. Methyllithium (89 mL, 1.7 M) was added dropwise to a solution of the acid **11** (12 g, 60.6 mmol; mp 105–110 °C; 0.5 M in THF) at −78 °C (internal temperature not exceeding −68 °C). The resulting dark orange solution was stirred for 12 h, quenched by pouring into 60 mL of 3 N HCl at 0 °C, and extracted with CH_2Cl_2 (2 × 100 mL), and the organic extracts were then evaporated to dryness. The resulting oil was dissolved in saturated Na_2CO_3 (40 mL) containing water (20 mL), and the aqueous solution was extracted with ether (100 mL). The aqueous phase was acidified with 6 N HCl (40 mL) and then extracted with CH_2Cl_2 (2 × 200 mL). The organic extract was dried first over Na_2SO_4 and second by filtration through $MgSO_4$ and then evaporated to an oil (10.55 g, 96% crude mass balance) consisting of the acids **12** and **11** in a ratio of 3:1 (NMR analysis), respectively.

This mixture of acids dissolved in CH_2Cl_2 was methylated with diazomethane (prepared in ether) at 0 °C, and the resulting mixture of the esters **4** and **9** was chromatographed on silica (100 g) by elution with 1:1 hexane/ether and then ether. From this chromatography there was obtained pure **4** (oil, 5.982 g) and pure **9** (oil, 2.89 g), which is a 77% overall yield of **4** from **11** based on recovered and reused ester **9**: R_f (silica) (ether) 0.63; IR ν_{max} 1735 (s, CO_2CH_3), 1695 (s, C=O), 1645 (m, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.20 (s, 3 H), 1.9–2.85 (m, 7 H); MS *m/e* 196 (30), 165 (9), 123 (100).

Preparation of the Pentalenedione 5. Sodium methoxide (1.08 mL of a 1 M solution in methanol) was added to benzene (12 mL), and the resulting mixture was distilled until the head temperature reached 80 °C. Ester **4** (0.212 g, 1.08 mmol) in a small amount of benzene was then added, and the resulting mixture was distilled (80 °C head temperature, 120 °C pot temperature) for 5 min. The mixture was rapidly cooled to 0 °C, poured into a saturated solution of potassium dihydrogen phosphate, stirred for 3 min, extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4 followed by filtration through $MgSO_4$, and then evaporated to a yellow waxy solid which on sublimation at 70 °C (10^{-6} mm) gave a white solid (0.115 g, 70%): mp 83–84 °C; R_f (silica) (1:1 ether/$CHCl_3$) 0.48, (ether) 0.39; IR ν_{max} 1760 (s, C=O), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.15 (s, 3 H), 2.28 (m, 4 H), 2.50 (d, 1 H), 3.20 (m, 1 H); MS *m/e* 164 (100), 136 (15), 135 (9), 122 (24), 121 (26), 108 (65). Anal. C, 73.16; H, 7.33.

Preparation of the Esters 14 and 15. To a solution of potassium hexamethyldisilizane (1.2 mmol, 1 M in THF) was added at −78 °C diketone **5** (200 mg, 1.2 mmol, 1 M in THF), and the resulting mixture was then stirred for 35 min before methyl iodoacetate (0.12 mL, 1.2 mmol) was added. The reaction was stirred at −78 °C for 20 min and then warmed to 0 °C and stirred for an additional 20 min. Saturated ammonium chloride (1 mL) was added to quench the reaction, which was then extracted with ether (3 × 2 mL). The organic extract was washed with 10% $NaHSO_3$ (1 mL), dried by filtration through $MgSO_4$, and evaporated to give essentially pure **14** as an oil (285 mg, ca. 99%). Preparation of the ester **15** from **5** and *tert*-butyl iodoacetate was carried out in the manner just described for **14**. Physical data for the esters **14** and **15** are as follows.

Compound **14**: R_f (silica) (ether) 0.74; IR ν_{max} 1755 (s, C=O), 1730 (m, CO_2CH_3), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.15 (s, 3 H), 2.30 (m, 4 H), 2.90 (AB q, J_{AB} = 18 Hz, $\Delta\nu_{AB}$ = 70.2, 2 H), 3.25 (m, 1 H), 3.60 (s, 3 H); MS *m/e* 236 (98), 205 (43), 194 (78), 177 (20), 176 (26), 163 (60), 135 (100).

Compound **15**: R_f (silica) (ether) 0.86; IR ν_{max} 1755 (s, C=O), 1730 (m, CO_2-*t*-Bu), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.4 (s, 9 H), 1.65 (s, 3 H), 2.15 (s, 3 H), 2.20 (m, 4 H), 2.83 (AB q, J_{AB} = 16 Hz, $\Delta\nu_{AB}$ = 62, 2 H), 3.25 (m, 1 H); MS *m/e* 278 (0), 222 (100), 206 (76), 180 (80), 135 (32), 122 (64).

Acknowledgment This research was supported by P.H.S. Grant CA-21496-01. Support from the Hoffmann-La Roche Foundation is gratefully acknowledged.

Registry No.—**4**, 67226-55-5; **5**, 67226-56-6; **7**, 3883-56-5; **9**, 67226-57-7; **10**, 67226-58-8; **11**, 67226-59-9; **12**, 67226-60-2; **14**, 67226-61-3; **15**, 67226-62-4; 2-methylcyclopentane-1,3-dione,765-69-5; methyl acrylate, 96-33-3; methyl iodoacetate, 5199-50-8; *tert*-butyl iodoacetate, 49827-15-8.

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(9) We thank Dr. Pius A. Wehrli of the Hoffmann-La Roche Co. for a generous sample of this material as well as an excellent experimental description for the preparation of it.
(10) The regiointegrity of this enolate was determined by quenching with DCl. This enolate undergoes alkylation reactions in excellent yield, and thus it parallels the behavior already found for the six-membered ring cases (ref 7).
(11) We have found that base treatment for 30 min at 0 °C brings about the retro-Michael reaction of **10** to the ester **9** and that hydrolysis of **9** occurs only at room temperature or above.
(12) Longer reaction times lead to products derived from the carboxylic acid portion of **11**.
(13) This excellent quenching procedure is described in ref 5.
(14) Other bases attempted for the cyclization of **4** into **5** include lithium and potassium methoxide, potassium *tert*-butoxide, lithium and potassium hexamethyldisilizane, and lithium diisopropylamide. The amide bases did not give cyclization products, and all of the alkoxide bases gave lower yields of **5** relative to sodium methoxide.

Cis to Trans Interconversion of Cyclic α-Hydroxy Epoxides

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During the course of pondering synthetic strategies directed toward the synthesis of the sesquiterpene eriolangin (**1**),[1] it occurred to us that the synthon **2** possessed a number of functional and stereochemical features potentially amenable to an expeditious resolution of this interesting problem. Mo-

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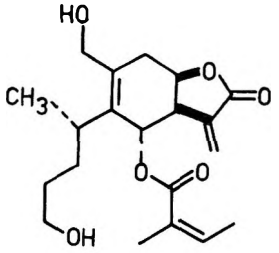
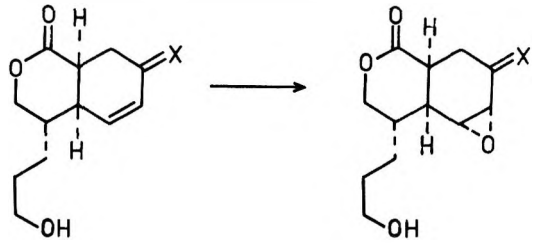


1

lecular models revealed that epoxidation of **2** would occur from the β face of the molecule if it occurred at all, and further that reduction of **2** would clearly result in formation of the α-allylic alcohol **3**. The latter reaction was not considered entirely without merit, however, for Henbest epoxidation of **3** should yield the *cis*-epoxy alcohol **4**,[2] from which the desired *trans*-

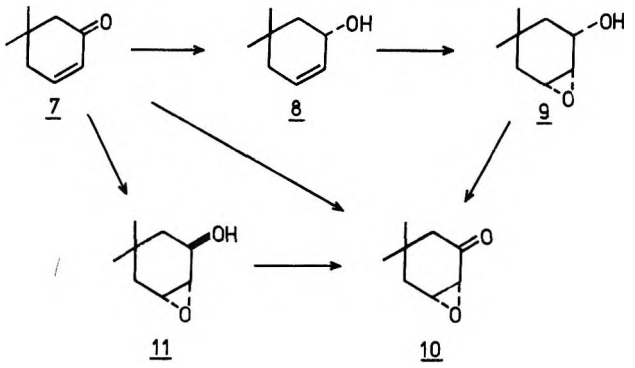


2, X = O
3, X = αOH, βH

4, X = αOH, βH
5, X = αH, βOH
6, X = O

epoxy alcohol **5** could, in principle, be obtained by oxidative conversion of **4** into the α-epoxy ketone **6** followed by stereospecific reduction of **6** into **5**. Elaboration of **5** into the *cis*-lactone functionality present in **1** could then be achieved using existing technology developed both by Danishesfky and ourselves.[3] We immediately commenced a search for methods applicable to the conversion of **4** → **6** → **5** but found, to our surprise, the literature to be exiguous in relevant analogies. It is the purpose of this note therefore to outline simple efficacious methodology germane to this problem.

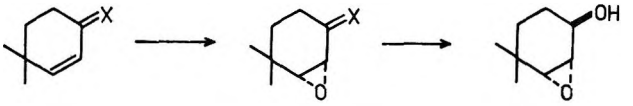
The enone **7** was reduced to the corresponding allylic alcohol **8** in the usual manner and then epoxidized with *m*-chloroperbenzoic acid to afford the α-hydroxy epoxide **9**.



7 **8** **9** **11** **10**

Several methods were considered for the oxidation of **9** into the desired epoxy ketone **10**, and while a number of methods partially succeeded, it was found that pyridinium chlorochromate buffered with sodium acetate[4] gave excellent yields of **10**. The authenticity of this material was established by hydrogen peroxide epoxidation of **7**, which gave a substance identical with **10**. A variety of reducing agents intended to give the *trans*-epoxy alcohol **11** from **10** were examined with highly variable success, the usual result being formation of mixtures of **11** and the *cis*-epoxy alcohol **9**. This lack of stereoselectivity in reduction was, however, finally overcome by employment of triisobutylaluminum as the reducing agent. With this reagent, stereospecific and high yield reduction of **10** into **11** was observed with the product being essentially uncontaminated with the epimeric alcohol **9**. The authenticity of **11**, prepared by the method described above, was confirmed by independent preparation of **11** from the enone **7** using the method described by Heathcock.[5,6]

A similar series of transformations has been carried out starting from the enone **12**, proceeding through the alcohol **13**, the epoxy alcohol **14**, and the epoxy ketone **15**, to finally yield the *trans*-epoxy alcohol **16**.



12, X = O
13, X = H, OH

14, X = H, OH
15, X = O

16

Since the reactions described herein are simple to carry out and proceed with high stereoselectivity, it seems reasonable to assume that this type of manipulative process could be applied to compound **2** as well as other synthetic intermediates intended to lead to sesquiterpene systems.

Experimental Section

General Section. Nuclear magnetic resonance (NMR) spectra were recorded at 100 MHz on a Jeolco Model JNM-MH-100 high-resolution spectrometer. Samples were examined in deuteriochloroform containing 1% by volume of tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrophotometer. Samples were analyzed in spectrograde chloroform solutions of 0.1 mm thickness. Mass spectra were obtained on a Dupont Model 21-940 B mass spectrometer.

Gas chromatography was performed on a Hewlett-Packard series 5700 A gas chromatograph with a series 5702 A temperature programmer and 5705 A thermal conductivity detector. The columns were either 6 ft × 0.125 in or 2 ft × 0.125 in aluminum tubing packed with 15% SE-30 on acid washed Chromosorb W, 80–100 mesh, and they were cured at 270 °C. The carrier gas was dry helium, and a flow rate of 20 ± 2 mL/min was maintained.

Chromatography was performed as follows. The silica, #7731 gel G type 60 for TLC, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under water aspirator vacuum, and the silica was repressed to avoid channeling between the glass and the silica. The compound was deposited with a minimal amount of solvent and then eluted with solvent using the water aspirator as a vacuum source.

Preparation of Alcohol 8. To a mixture of lithium aluminum hydride (0.30 g, 8.0 mmol) in ether (20 mL) at 0 °C was slowly added the enone **7** (1.0 g, 8.0 mmol). After stirring the resulting mixture for 15 min, saturated Na_2SO_4 (1 mL) was added followed by water (0.5 mL). The suspension was diluted with ether, stirred for 1 h, filtered through $MgSO_4$, and then evaporated to yield the allylic alcohol **8** (0.90 g, 88%): retention time (150 °C–2 min, 32 °C/min to 250 °C–6 min), 1.3 min; IR ν_{max} 3400 cm^{-1} (broad, OH); NMR δ 0.90 (s, 3 H), 1.00 (s, 3 H), 1.00–2.00 (m, 4 H), 2.50–3.50 (broad, OH), 4.20 (m, 1 H), 5.70 (s, 2 H); MS *m/e* 126.

Preparation of the *cis*-Epoxy Alcohol 9. To a solution of *m*-chloroperbenzoic acid (0.70 g, 4.2 mmol, 1.3 equiv, 99%) in methylene chloride (10 mL) at 0 °C was added over a period of 4 min the allylic alcohol **8** (0.40 g, 3.1 mmol). The resulting solution was stirred for 15 min at 0 °C and then for 12 h at room temperature. The precipitated *m*-chlorobenzoic acid that formed during the reaction was filtered off and washed with methylene chloride (5 mL). Ether (30 mL) was added to the filtrate, which was then washed with freshly prepared saturated $NaHSO_3$ (2 × 10 mL) and saturated $NaHCO_3$ (3 × 10 mL), filtered through $MgSO_4$, and evaporated to dryness to yield crude **9** (0.39 g, 88%). This material was chromatographed using silica (10 g) eluting with 1:1 ether/hexane to give pure **9** (0.250 g, 57%): retention time (150 °C–2 min, 32 °C/min to 250 °C–6 min), 1.4 min; IR ν_{max} 3350 cm^{-1} (broad, OH); NMR δ 0.85 (s, 3 H), 0.91 (s, 3 H), 1.00–1.60 (m, 2 H), 1.60 (s, 2 H), 2.60 (OH), 3.40 (s, 2 H), 4.18 (m, 1 H); MS *m/e* 142.

Preparation of the Keto Epoxide 10. To methylene chloride (2.5 mL) was added **9** (93 mg, 0.65 mmol), sodium acetate (100 mg, 2.0 equiv, 1.3 mmol), and pyridinium chlorochromate (280 mg, 2.0 equiv, 1.3 mmol). The resulting orange suspension became brown within 2 min, and the reaction was stirred for 6 h at room temperature. Ether

(5 mL) was added, and stirring was continued for 10 min, whereupon the organic solvent was decanted from the oily brown sludge present in the reaction mixture. Ether (2 × 5 mL) was used to wash the brown residue, and the combined organic solutions were then filtered through a Florisil/$MgSO_4$ pad. Evaporation of the filtrate gave pure **10** (78 mg, 80%): retention time (130 °C–2 min, 32 °C/min to 250 °C–6 min), 1.40 min; IR ν_{max} 1710 cm^{-1} (s, C=O); NMR δ 0.95 (s, 3 H), 1.08 (s, 3 H), 1.65–2.15 (m, 3 H), 2.65 (d, 1 H), 3.19 (d, 1 H), 3.46 (t, 1 H); MS *m/e* 140.

Preparation of the *trans*-Epoxy Alcohol 11. To a solution of **10** (100 mg, 0.72 mmol) in toluene (2 mL) at 0 °C was added over a period of 5 min triisobutylaluminum (Texas Alkyls; 1.23 M in toluene, 0.60 mL, 1 equiv). The solution was stirred for 15 min and then quenched by the successive addition of methanol (0.3 mL), saturated NH_4Cl (0.3 mL), ether (6 mL), and Celite (0.5 g). This mixture was stirred for 1 h and then filtered through a $MgSO_4$ pad, and the filtrate was evaporated to give **11** (98% pure by GC and NMR; 101 mg, 99%): retention time (130 °C–2 min, 32 °C/min to 250 °C–6 min), 2.0 min; IR ν_{max} 3460 cm^{-1} (broad, OH); NMR δ 0.90 (s, 3 H), 0.98 (s, 3 H), 1.00–1.82 (m, 4 H), 2.75 (OH), 3.07 (d, 1 H), 3.20 (t, 1 H), 4.09 (m, 1 H); MS *m/e* 142.

Preparation of the Allylic Alcohol 13. To a stirred suspension of lithium aluminum hydride (320 mg, 8.0 mmol) in ether (14 mL) was slowly added at room temperature a solution of the enone **12** (2.0 g, 16.1 mmol) in ether (16 mL). After the addition was complete, the reaction mixture was stirred for 1 h and then cooled to 0 °C and quenched with saturated sodium sulfate. The resulting mixture was filtered through $MgSO_4$ and the solvent evaporated to give **13** (1.64 g, 82%): IR ν_{max} 3600 (s, OH), 3450 (broad, OH) cm^{-1}; NMR δ 1.20–1.80 (m, 4 H), 1.95 (s, 3 H), 1.95 (OH), 2.05 (s, 3 H), 5.60 (m, 2 H); MS *m/e* 126.

Preparation of the *cis*-Epoxy Alcohol 14. To a solution of **13** (785 mg, 6.23 mmol) in methylene chloride (7 mL) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (1.60 g, 9.35 mmol, 85%) in methylene chloride (15 mL) and ethyl acetate (3.5 mL). The resulting mixture was stirred at 0 °C for 8 h and then quenched with 5% sodium hydroxide (28 mL) and extracted with methylene chloride (4 × 15 mL). The combined extracts were filtered through $MgSO_4$ and evaporated to an oil. Chromatography of this oil on silica eluting with 2:1 ether/hexane gave pure **14** (565 mg, 64%): retention time (120 °C–2 min, 32 °C/min to 250 °C–6 min), 1.52 min; R_f (2:1 hexane/ether) 0.175; IR ν_{max} 3350 cm^{-1} (broad, OH); NMR δ 1.00 (s, 3 H), 1.05 (s, 3 H), 1.20–1.42 (m, 4 H), 2.60 (m, 1 H), 2.90 (d, 1 H), 3.30 (t, 1 H), 3.92 (OH); MS *m/e* 142.

Preparation of the Keto Epoxide 15. Pyridinium chlorochromate (378 mg, 1.75 mmol), alcohol **14** (100 mg, 0.877 mmol), sodium acetate (143 mg, 1.74 mmol), and methylene chloride (1.8 mL) were stirred at room temperature for 6 h. The organic solution was decanted, and the remaining brown residue was washed with methylene chloride (3 × 5 mL). The combined organic washes were filtered through Florisil and then evaporated to give pure **15** (88 mg, 88%): retention time (120 °C–2 min, 32 °C/min to 250 °C–6 min), 1.92 min; R_f (hexane/ether, 2:1) 0.55; IR ν_{max} 1710 cm^{-1} (s, C=O); NMR δ 1.04 (s, 3 H), 1.25 (s, 3 H), 1.80–2.60 (m, 4 H), 3.30 (s, 2 H); MS *m/e* 140.

Preparation of the *trans*-Epoxy Alcohol 16. To **15** (100 mg, 0.714 mmol) in toluene (1.5 mL) at 0 °C was slowly added triisobutylaluminum (0.638 mL, 1.23 M in toluene), and the resulting mixture was stirred at 0 °C for 40 min. The reaction mixture was diluted with ether (4 mL) and then quenched by the addition of methanol (0.5 mL), saturated NH_4Cl (1 mL), and Celite. After stirring for 1 h, the mixture was filtered through $MgSO_4$ and the filtrate was evaporated to dryness, giving **16** (93 mg; 93% pure by GC and NMR analysis): retention time (120 °C–2 min, 32 °C/min to 250 °C–2 min), 1.52 min; R_f (hexane/ether, 2:1) 0.175; IR ν_{max} 3460 cm^{-1} (broad, OH); NMR δ 1.00 (two overlapping singlets, 6 H), 1.15–1.70 (m, 4 H), 2.65, (d, 1 H), 2.95 (d, 1 H), 3.30 (OH), 3.85 (t, 1 H); MS *m/e* 142.

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Registry No.—**7**, 4694-17-1; **8**, 25866-56-2; **9**, 38309-46-5; **10**, 17421-93-1; **11**, 66036-65-5; **12**, 1073-13-8; **13**, 5020-09-7; **14**, 38309-45-4; **15**, 1074-26-6; **16**, 66036-66-6.

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Reaction of *tert*-Butyldimethylsilyl Esters with Oxalyl Chloride–Dimethylformamide: Preparation of Carboxylic Acid Chlorides under Neutral Conditions

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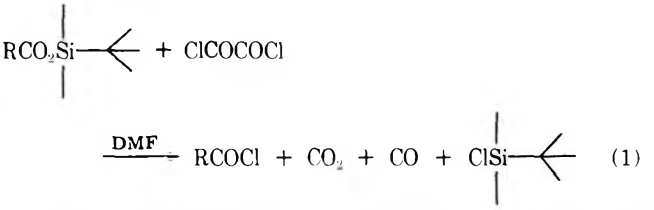
One of the more common transformations encountered in organic synthesis is the conversion of a carboxylic acid to the corresponding carboxylic acid chloride. Most current methods[1] which accomplish this conversion involve acidic conditions and consequently, if a carboxylic acid contains an acid sensitive functionality, it is likely that the desired carboxylic acid chloride may be obtained in low yield or not at all. In this communication we describe a new method for forming carboxylic acid chlorides under neutral conditions.

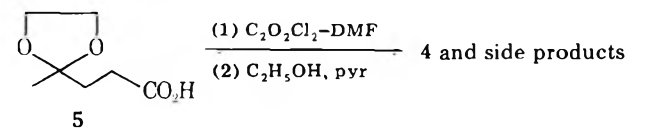
The *tert*-butyldimethylsilyl group has recently been reported to be of value as a protecting group for alcohols and carboxylic acids.[2] Furthermore, the report of the conversion of trimethylsilyl pyruvate to its corresponding acid chloride[3] encouraged us to investigate the reaction of *tert*-butyldimethylsilyl esters with oxalyl chloride in the presence of a catalytic amount of dimethylformamide (DMF) as a potential method of forming carboxylic acid chlorides under neutral conditions (eq 1).



(1)

Treatment of *tert*-butyldimethylsilyl heptanoate (**1**) with 1.2 equiv of oxalyl chloride in methylene chloride in the presence of a catalytic quantity of DMF resulted in slow gas evolution over a period of 2 h. Removal of the solvent and exposure of the resulting acid chloride to ethanol in pyridine gave ethyl heptanoate (**2**) in 92% yield. In a similar manner, treatment of the various *tert*-butyldimethylsilyl esters listed in Table I with oxalyl chloride–DMF gave, after treatment of the resulting acid chlorides with ethanol–pyridine, the respective ethyl esters in the indicated isolated yields.

The results presented in Table I indicate that this reaction will tolerate an acid sensitive functionality quite well. For example, while the conversion of the *tert*-butyldimethylsilyl ester **3** which contains an acid sensitive ketal moiety to the ethyl ester **4** proceeds in excellent yield, the reaction of the corresponding carboxylic acid **5**[4] with oxalyl chloride–DMF



5

under identical conditions followed by the reaction with ethanol–pyridine gives **4** in much lower yield; moreover the product is accompanied by at least three additional less volatile side products (see Experimental Section).

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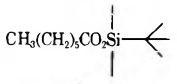
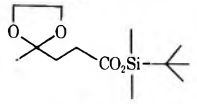
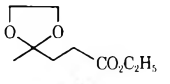
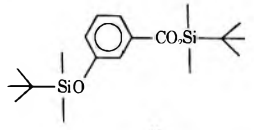
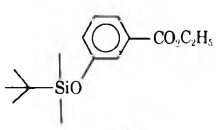
Table I. Ethyl Esters Prepared [a]

tert-butyldimethylsilyl ester	registry no.	ethyl ester	reigstry no.	% yield [b]
 1	54251-63-7	$CH_3(CH_2)_5CO_2C_2H_5$ 2	106-30-9	92
 3	67226-75-9	 4	941-43-5	95
 6	67226-76-0	 8	67226-78-2	87
 7	67226-77-1	 9	67226-79-3	98

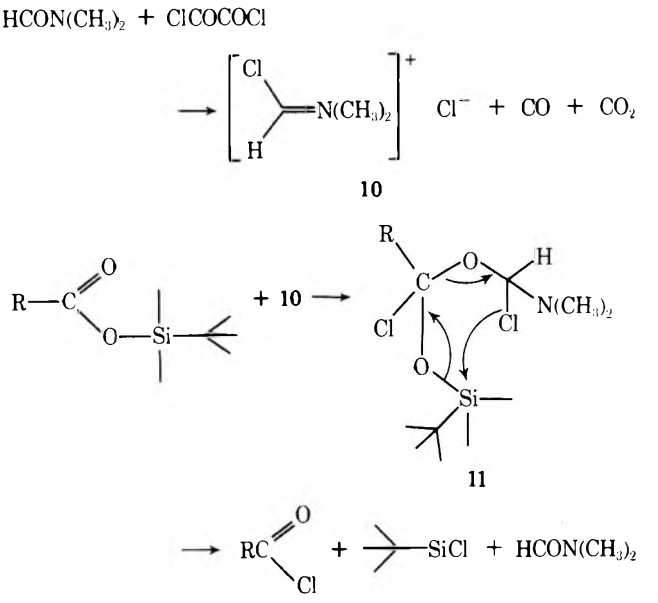
[a] See Experimental Section for conditions. [b] Yields are for distilled products.

Since we have found that *tert*-butyldimethylsilyl ethers are usually stable to oxalyl chloride–DMF under reaction conditions which lead to acid chloride formation and since both the hydroxyl and carboxylate moieties of a hydroxy acid can be silylated in a single step, this method is particularly useful for the preparation of carboxylic acid chlorides which are derived from hydroxy substituted carboxylic acids as illustrated with the bissilylated hydroxy acids **6** and **7** which were converted via the corresponding acid chlorides to the ethyl esters **8** and **9**, respectively, in excellent yields.

Control experiments employing **7** have demonstrated that acid chloride formation proceeds extremely slowly in the absence of DMF; this implicates dimethylformiminium chloride[5] (**10**) as the reactive species. Conceivably, the mechanism for the transformation of a *tert*-butyldimethylsilyl ester to a carboxylic acid chloride could involve addition of dimethylformiminium chloride to the carboxyl group of the silyl ester to give intermediate **11** or a formal equivalent which undergoes fragmentation as postulated to generate *tert*-butyldimethylchlorosilane, DMF, and the carboxylic acid chloride (Scheme I).

Thus, the reaction of a *tert*-butyldimethylsilyl ester with oxalyl chloride in the presence of a catalytic amount of DMF is an effective method for the preparation of carboxylic acid chlorides under neutral conditions. Furthermore, particularly for the preparation of less volatile acid chlorides, this method has a distinct advantage over the triphenylphosphine–carbon tetrachloride procedure[6] which is commonly employed for this purpose since unlike the latter method, which results in the formation of an equivalent of triphenylphosphine oxide, the side products (*tert*-butyldimethylchlorosilane, CO, and CO_2) in this case are volatile and can be removed with ease. Of equal importance, this procedure provides a facile method of preparing carboxylic acid chlorides derived from hydroxy substituted carboxylic acids. In this respect, this reaction is likely to show advantages over the carboxylic acid sodium salt–oxalyl chloride method[7] since activation of the carboxylate group for acid chloride formation and protection of the hydroxy moiety can be accomplished in a single silylation step whereas the latter procedure as applied to hydroxy acids would require separate protection and sodium salt formation steps. Furthermore, it is likely that for many situations, the preparation of an easily purified (distillation or recrystallization) silyl ester would be more convenient then the preparation of a carboxylic sodium salt which in some cases might be hydroscopic, difficult to dry, or have low solubility in reaction media.

Scheme I



Experimental Section

General Procedure for the Preparation of *tert*-Butyldimethylsilyl Esters: *tert*-Butyldimethylsilyl Heptanoate (1). To a solution of 13.0 g (100 mmol) of heptanoic acid and 15.82 g (105 mmol) of *tert*-butyldimethylchlorosilane in 20 mL of dry DMF was added 13.96 g (205 mmol) of imidazole. The solution was stirred overnight, poured into H_2O, and extracted with petroleum ether. The organic solution was washed with a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed and the residue was distilled (95–100 °C (1.5 mm)) giving 21.0 g (86%) of **1**: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.30 (t, 2 H, CH_2CO), 1.30 (m, 8 H, $-(CH_2)_4-$), 0.97 (s, 12 H, $SiC(CH_3)_3$, terminal CH_3), 0.27 (s, 6 H, $Si(CH_3)_2$); IR (neat) 1730 cm^{-1}.

Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.54. Found: C, 64.10; H, 11.46.

***tert*-Butyldimethylsilyl 2-Methyl-1,3-dioxolan-2-propionate (3).** This was prepared from 7.0 g (44 mmol) of **5**,[4] 7.2 g (48 mmol) of *tert*-butyldimethylchlorosilane, and 5.95 g (87 mmol) of imidazole in 19 mL of DMF (60 °C, 4 h) which gave after molecular distillation (bath temperature 125 °C (0.3 mm)) 10.2 g (85%) of **3** as a colorless liquid: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.86 (s, 4 H, OCH_2CH_2O), 2.13 (m, 4 H, $(CH_2)_2CO$), 1.26 (s, 3 H, CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 6

H, $Si(CH_3)_2$); IR (neat) 1724 cm^{-1}; MS calcd for $C_{12}H_{23}O_4Si$ (m-H_2O), 259.1365 (found, 259.1355).

Anal. Calcd for $C_{13}H_{26}O_4Si$: C, 56.89; H, 9.55. Found: C, 56.73; H, 10.06.

***tert*-Butyldimethylsilyl *tert*-Butyldimethylsilyloxyacetate (6).** This was prepared from 10.0 g (130 mmol) of glycolic acid, 40.6 g (270 mmol) of *tert*-butyldimethylchlorosilane, and 36.3 g (530 mmol) of imidazole in 80 mL of DMF (25 °C, 18 h) to give after removal of solvent and drying under vacuum 39.2 g (98%) of **6** as a white solid: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 4.14 (s, 2 H, OCH_2), 0.87 (s, 18 H, $C(CH_3)_3$), 0.22 (s, 6 H, Si $(CH_3)_2$), 0.04 (s, 6 H, Si $(CH_3)_2$); IR (KBr) 1748 cm^{-1}.

Anal. Calcd for $C_{14}H_{32}O_3Si_2$: C, 55.21; H, 10.59.

***tert*-Butyldimethylsilyl *m*-(*tert*-Butyldimethylsilyloxybenzoate) (7).** This was prepared from 10.0 g (72 mmol) of m-hydroxybenzoic acid, 22.9 g (152 mmol) of *tert*-butyldimethylchlorosilane, and 19.7 g (290 mmol) of imidazole (50–60°, 5 hr) to give after molecular distillation (bath temperature 170 °C (1.0 mm)) 25.5 g (98%)) of **7**: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 7.44, 7.22, 7.00 (m's, 4 H, aromatic), 0.96 (s, 9 H, $C(CH_3)_3$), 0.93 (s, 9 H, $C(CH_3)_3$), 0.32 (s, 6 H, $Si(CH_3)_2$), 0.16 (s, 6 H, $Si(CH_3)_2$); IR (neat) 1703 cm^{-1}.

Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.24; H, 9.35. Found: C, 62.11; H, 9.28.

General Procedure for the Reaction of *tert*-Butyldimethylsilyl Esters with Oxalyl Chloride–DMF: Ethyl Heptanoate (2). To a solution of 10.0 g (41 mmol) of **1** in 40 mL of CH_2Cl_2 containing 4 drops of DMF was added dropwise 4.5 mL (51 mmol) of oxalyl chloride at 0 °C. After stirring 1.5 h at 0 °C and 0.5 h at room temperature, the solvent was removed. To the residue was slowly added a mixture of 10 mL of ether, 10 mL of pyridine, and 10 mL of ethanol. After stirring 1 h, the mixture was diluted with ether and filtered. The solvents were removed and the residue was distilled twice to give 5.98 g (92%) of **2**: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 4.12 (q, 2 H, OCH_2CH_3), 2.28 (t, 2 H, CH_2CO), 2.70–2.10 (m, 8 H, $-(CH_2)_4-$), 1.22 (t, 3 H, OCH_2CH_3), 0.87 (m, 3 H, terminal CH_3).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.00; H, 11.82.

Heptanoyl Chloride. The above reaction was repeated without the addition of ethanol–pyridine. The CH_2Cl_2 was removed and the residue was distilled under aspirator pressure giving a low-boiling fraction (40–43 °C) consisting of *tert*-butyldimethylchlorosilane and a higher boiling fraction (70–73 °C) consisting of 5.2 g (86%) of heptanoyl chloride. Both compounds were identified by comparison of their ^1H NMR spectrum with that of authentic samples.

Ethyl 2-Methyl-1,3-dioxolan-2-propionate (4). This was prepared from 5.1 g (19 mmol) of **3** and 2.72 g (21 mmol) of oxalyl chloride in 19 mL of CH_2Cl_2 containing 3 drops of DMF. After a 1.25-h reaction time, ethanol–pyridine quenching, and molecular distillation (bath temperature 90–110 °C (0.5 mm)), 3.3 g (95%) of **4** was obtained: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 4.10 (q, 2 H, CH_2CH_3), 3.90 (s, 4 H, OCH_2CH_2O), 2.17 (m, 4 H, $(CH_2)_2CO$), 1.28 (s, 3 H, CH_3), 1.22 (t, 3 H, CH_2CH_3); IR (neat) 1740 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.68; H, 8.49.

Ethyl *tert*-Butyldimethylsilyloxyacetate (8). This was obtained from 15.0 g (49 mmol) of **6** and 7.2 g (57 mmol) of oxalyl chloride in 60 mL of CH_2Cl_2 containing 10 drops of DMF. After a reaction time of 3 h, ethanol–pyridine quenching, and molecular distillation (bath temperature 110–120 °C (25 mm)), 9.24 g (87%) of **8** was obtained: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 4.17 (s, 2 H, OCH_2), 4.16 (q, 2 H, CH_2CH_3), 1.20 (t, 3 H, CH_2CH_3), 0.84 (s, 9 H, $SiC(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); IR (neat) 1760 cm^{-1}.

Anal. Calcd for $C_{10}H_{22}O_3Si$: C, 55.00; H, 10.15. Found: C, 54.63; H, 10.42.

Ethyl *m*-(*tert*-Butyldimethylsilyloxy)benzoate (9). This was prepared from 6.0 g (16 mmol) of **8** and 2.0 mL (23 mmol) of oxalyl chloride in 13 mL of CH_2Cl_2 containing 6 drops of DMF. After a 40 h reaction time, quenching with ethanol–pyridine, and molecular distillation (bath temperature 115 °C (0.4 mm)), 4.51 g (98%) of **9** was obtained: ^1H NMR δ_{Me_4Si} ($CDCl_3$) 7.40, 7.16, 6.88 (m's, 4 H, aromatic), 4.26 (q, 2 H, CH_2CH_3), 1.28 (t, 3 H, CH_2CH_3), 0.90 (s, 9 H, $C(CH_3)_3$), 0.12 (s, 6 H, $Si(CH_3)_2$); IR (neat) 1724 cm^{-1}; MS calcd for $C_{15}H_{24}O_3Si$, 280.1494 (found, 280.1485).

Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 63.83; H, 8.54.

Reaction of 2-Methyl-1,3-dioxolan-2-propionic Acid (5) with Oxalyl Chloride–DMF. To a solution of 1.0 g (6.3 mmol) of **5**[4] in 4 mL of CH_2Cl_2 containing 2 drops of DMF was added 0.61 mL (7.0 mmol) of oxalyl chloride. The solution was stirred at room temperature for 1 h. The solvent was removed and a mixture of 1.3 mL of ethanol and 2.6 mL of pyridine was added. After stirring 15 min, the solution was poured into a saturated solution of $NaHCO_3$ and extracted with ether. The ether solution was dried over Na_2SO_4. The solvent was removed. The residue was distilled (bath temperature 90–110 °C (0.5 mm)) to give 0.28 g of distillate and 0.28 g of pot residue.

TLC ($CHCl_3$–ether, 19:1) of the distillate indicated that it consisted of **4** and three additional more polar components; the pot residue consists only of the more polar side products.

Acknowledgments. We wish to thank Mr. L. Brancone and staff for microanalyses and Messrs. W. Fulmor and G. Morton and Dr. R. T. Hargreaves and staff for spectral data.

Registry No.—5, 4388-57-2; heptanoic acid, 111-14-8; *tert*-butyldimethylchlorosilane, 18162-48-6; glycolic acid, 79-14-1; m-hydroxybenzoic acid, 99-06-9; oxalyl chloride, 79-37-8; dimethylformamide, 68-12-2; heptanoyl chloride, 2528-61-2.

References and Notes

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Synthesis of 2-Methyl-1-cyclopentene-1-carboxylate Esters. Reaction of Cuprates with β-Substituted Cyclopentenecarboxylates

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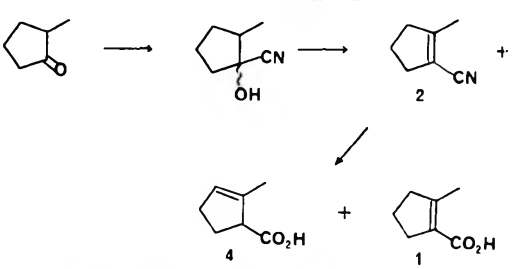
Received March 13, 1978

In connection with other synthetic work we had need for an efficient synthesis of 2-methyl-1-cyclopentene-1-carboxylic acid (**1**). The classical procedure[1] for preparation of this material (Scheme I) involves addition of cyanide to 2-methylcyclopentanone, dehydration of the resulting cyanohydrin, and hydrolysis to the acid. Recent studies[2] have shown that this procedure gives a mixture of acids, since dehydration of the cyanohydrin gives both unsaturated nitriles **2** and **3**. We found[3] that even after separation of pure nitrile **2**, hydrolysis gave a mixture of acid **1** and the nonconjugated isomer **4**,[4] from which acid **1** could be isolated by crystallization.[5]

The inefficiency of the above procedure, which requires a somewhat expensive starting material, led us to investigate new methods for synthesis of acid **1**. Subsequent to the development of the methodology described below, another method for synthesis of the ethyl-2-methyl-1-cyclopentene-1-carboxylate (**6**) was described[6] (Scheme II) based upon methodology reported by Büchi. By this method, ester **6** can be prepared from keto ester **5** in 46% yield. Keto ester **5** was prepared from 2-methycyclohexanone in two steps in unreported yield.[8] The reports by Casey[9] that acyclic β-acyloxy

Scheme I



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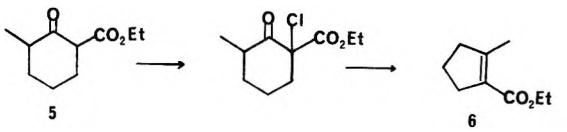
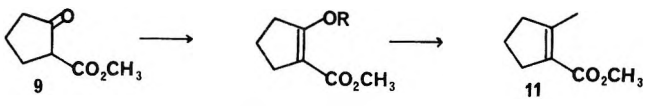
Scheme II



Scheme III

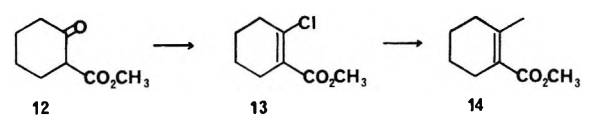


10a, R = $COCH_3$
10b, R = COPh
10c, R = $COPhOCH_3$
10d, R = CO_2Et
10e, R = $COPh(CH_3)_3$
10f, R = $COC(CH_3)_3$

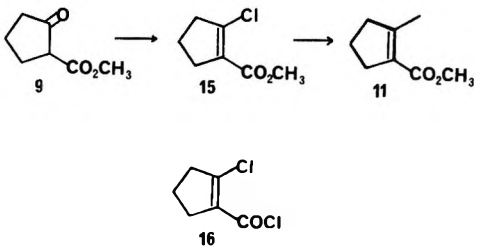
α,β-unsaturated esters were readily converted to the corresponding β-methyl α,β-unsaturated esters (e.g., 7 → 8) by treatment with lithium dialkylcuprates suggested a route to ester 11 involving a similar reaction with derivatives of the readily available 2-carbomethoxycyclopentanone (Scheme III).

2-Carbomethoxycyclopentanone (9) was converted in excellent yield into the enol acetate derivative **10a** by treatment with isopropenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid.[9] Treatment of **10a** with an excess of lithium dimethylcuprate according to Casey's procedure gave only cyclopentanone **9** as a product. This product was observed with either acidic workup or workup using methanol. The corresponding benzoate, **10b**, was prepared by treating ketone **9** with benzoyl chloride and triethylamine in HMPA at −5 °C.[9c] Reaction of this ester with lithium dimethylcuprate did give the desired β-methyl α,β-unsaturated ester **11** in 50% yield. Analysis of the crude product indicated the presence of acetophenone and methyl benzoate as major byproducts. The different results with **10a** and **10b** suggested the possibility that addition of the cuprate to these cyclic derivatives was slower than to the acyclic analogues resulting in significant attack on the enol ester either by the cuprate reagent or by the alkoxide always present to some extent in the methyllithium used to prepare the cuprate. We then investigated a series of enol ester derivatives (**10c–f**) to determine the effect of further changes in the enol ester functionality. Reaction of esters **10c** and **10d** with lithium dimethylcuprate gave the desired product in yields of 60 and 50%, respectively. The yield with ester **10e** was only 36%. In this case starting enol ester **10e** was recovered even after long reaction time. Thus, in this case, cleavage of the enol ester group was prevented, but the desired reaction appeared to be slowed also. The best enol ester derivative found for this conversion was ester **10f**. Reaction **10f** with 2 equiv of lithium dimethylcuprate gave ester **11** in 71% yield. The yield for the two-step conversion of **9** to **11** was 55%. Thus, the procedure outlined in Scheme III is reasonably effective, provided a suitable enol ester derivative is chosen.

The report by Clark and Heathcock[10] that lithium dimethylcuprate converted methyl 2-chloro-2-cyclohexene-1-carboxylate (**13**) into methyl 2-methyl-1-cyclohexene-1-carboxylate (**14**) in quantitative yield led us to investigate this type of procedure for preparation of ester **11**. The problem with this procedure is to find a method for obtaining the requisite chloro derivative. Heathcock[10] has shown that his oxalyl chloride procedure for β-dicarbonyl systems did not convert keto ester **12** to **13**. Other reagents such as phosphorus trichloride, phosphorus oxychloride, and thionyl chloride are also unsatisfactory for this conversion.



Scheme IV



In 1935, Rapson and Robinson[11] reported the synthesis of ethyl 2-chloro-1-cyclopentene-1-carboxylate in 45% yield by the treatment of 2-carbethoxycyclopentanone with phosphorus pentachloride in petroleum ether at 55 °C. Our attempts to apply this reaction to 2-carbomethoxycyclopentanone (**9**) gave the chloro derivative **15** in even lower yields. However, by a modification of this procedure, we have improved the yield significantly. Treatment of keto ester **9** with phosphorus pentachloride in anhydrous hexane or benzene for 2 h at 60–65 °C followed by addition of methanol to the cooled reaction mixture gave, after normal workup, chloro ester **15** in 80% yield. It is known that esters can be converted into acid chlorides by vigorous treatment with phosphorus pentachloride. Thus, the addition of methanol is necessary to convert any acid chloride **16** in the reaction mixture into the desired ester **15**. Reaction of chloro ester **15** with 1.1 equiv of lithium dimethylcuprate gave ester **11** in quantitative yield. Thus, the procedure of choice for synthesis of this cyclopentene ester is that shown in Scheme IV. Hydrolysis of ester **11** gave the carboxylic acid **1** in excellent yield.[12]

Experimental Section

General Procedures. Infrared spectra were determined on a Perkin-Elmer Model 327B or on a Beckman Instruments Model IR8 infrared spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were determined on Varian Associates Model HA-100, T-60, or EM-360 spectrometers in the solvent indicated. Carbon-13 NMR spectra were obtained in $CDCl_3$ solution in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. Tetramethylsilane (Me_4Si) was used as the internal reference for all spectra except where stated otherwise. Chemical shifts are reported on the δ scale in parts per million downfield from Me_4Si for all spectra. High-resolution mass spectra were determined on a CEC Model 21-110B spectrometer under the supervision of Dr. R. Grigsby.

Vapor phase chromatographic (VPC) analyses were performed on a Hewlett-Packard Instrument, Model 700, equipped with a thermal conductivity detector with helium as the carrier gas, or on a Varian Aerograph Model 940 equipped with a flame ionization detector with nitrogen as the carrier gas. Column chromatography was performed using EM Reagents silica gel (60–200 mesh) or Grace silica gel (60–200 mesh).

Anhydrous ether was distilled from lithium aluminum hydride prior to use. Hexane and benzene were distilled from sodium–benzophenone.

"Bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate. "Brine" refers to a saturated aqueous solution of sodium chloride. "Concentration" refers to the removal of solvent by rotary evaporation (Büchi Rotovapor) at 60 mmHg. "Evaporative distillation" refers to bulb-to-bulb (Kugelrohr) short-path distillation in which the bulb was heated in an air oven. The temperatures cited for

these distillations refer to the maximum temperature attained by the air chamber during the distillation.

Preparation of Enol Esters. Methyl 2-Acetoxy-1-cyclopentene-1-carboxylate (10a). A mixture of 2-carbomethoxycyclopentanone (**9**) (28.4 g, 0.2 mol), 75.0 g (0.75 mol) of isopropenyl acetate, and 1.0 g of *p*-toluenesulfonic acid monohydrate was heated at 110 °C for 12 h. The excess isopropenyl acetate and the acetone formed in the reaction were removed at reduced pressure, and the residue was distilled at 93 °C (1.7 mm) to give 33.54 g (91%) of enol acetate **10a**: IR (film) 1750, 1710, 1650 cm^{-1}; ^1H NMR (CCl_4) δ 3.62 (s, 3 H, CO_2CH_3), 2.45–2.75 (m, 4 H), 2.12 (s, 3 H, $OCCH_3$), 1.75–2.10 (m, 2 H).

General Procedure for Esters 10b–f. All other enol esters were prepared by the treatment of keto ester **9** with the appropriate acid chloride and triethylamine in hexamethylphosphoric triamide.[9c] Freshly distilled acid chloride (1.1 equiv) was added dropwise to a stirred solution of keto ester **9** (1.0 equiv) and triethylamine (1.1 equiv) in hexamethylphosphoric triamide at −5 °C. The reaction mixture was then brought to room temperature and stirred overnight. The reaction mixture was quenched with water (or bicarbonate) and ether and the separated aqueous layer was extracted with ether. The combined ether extracts were washed (water and brine), dried over $MgSO_4$, concentrated, and distilled at reduced pressure to give the enol ester. Each product was checked for purity by VPC analysis and characterized by a combination of spectral (IR, ^1H NMR, MS) and analytical data. Boiling points, yields, and ^1H NMR data are given below:

Methyl 2-Benzoyloxy-1-cyclopentene-1-carboxylate (10b): 124 °C (0.16 mm); 85% yield; ^1H NMR (CCl_4) δ 1.80–2.95 (m, 6 H), 3.60 (s, 3 H, CO_2CH_3), 7.20–7.60 (m, 3 H, aromatic H), and 7.90–8.20 (m, 2 H, aromatic H).

Methyl 2-Anisoyloxy-1-cyclopentene-1-carboxylate (10c): 140 °C (0.01 mm); mp 45–46 °C; 68% yield; ^1H NMR (CCl_4) δ 1.80–2.95 (m, 6 H), 3.60 (s, 3 H, CO_2CH_3), 3.80 (s, 3 H, $ArOCH_3$), 6.84 (2 H, aromatic H), and 7.98 (2 H, aromatic H).

Methyl 2-Ethoxycarbonyloxy-1-cyclopentene-1-carboxylate (10d): 74 °C (0.06 mm); 89% yield; ^1H MNR (CCl_4) δ 1.37 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.65–2.80 (m, 6 H), 3.64 (s, 3 H, CO_2CH_3), 4.20 (q, J = 7 Hz, 2H, OCH_2CH_3).

Methyl 2-Mesitoyloxy-1-cyclopentene-1-carboxylate (10e): 140 °C (0.2 mm); 91% yield; ^1H NMR (CCl_4) δ 1.80–2.95 (m, 15 H), 3.66 (s, 3 H, CO_2CH_3), and 6.82 (bs, 2 H, aromatic H).

Methyl 2-Pivaloyloxy-1-cyclopentene-1-carboxylate (10f): 79 °C (0.6 mm); 78% yield; ^1H NMR (CCl_4) δ 1.27 (s, 9 H, $C(CH_3)_3$), 1.72–2.78 (m, 6 H), and 3.64 (s, 3 H, CO_2CH_3).

Reaction of Enol Esters with Lithium Dimethylcuprate. Lithium Dimethylcuprate.[13] To a cooled (−5 to 0 °C), stirred suspension of CuI (3.81 g, 20 mmol) in 60 mL of anhydrous ether under an atmosphere of nitrogen was added 20 mL of 2.0 M ethereal methyllithium (Aldrich, 40 mmol). Upon the addition of 1 equiv of methyllithium a bright yellow methylcopper solid was formed; the methylcopper dissolved when the second equivalent of methyllithium was added to give a colorless to pale pink solution of lithium dimethylcuprate (~20 mmol).

Reaction of Enol Benzoate 10b with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of lithium dimethylcuprate (20 mmol) was added 2.46 g (10 mmol) of enol benzoate **10b.** The reaction was maintained at −20 °C for 2.5 h, then quenched with 3 N HCl. The copper salt was filtered, and the aqueous layer was extracted twice with 50-mL portions of ether. The combined ethereal solution was washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated to give 1.20 g of crude product. The VPC analysis on 3% SE-30 showed the product contained the methylated ester **11**, β-keto ester **9**, acetophenone, and methyl benzoate. The crude product was chromatographed (silica gel) and evaporatively distilled at 55 °C (2.0 mm) to give 800 mg (54% yield) of ester **11**: IR (film) 1720 (C=O), 1650 (C=C) cm^{-1}; ^1H NMR δ 1.60–2.80 (m, 9 H) and 3.65 (s, 3 H, CO_2CH_3); ^{13}C NMR δ 16.2 (C-2 CH_3), 21.5 (C-4), 33.6 and 40.8 (C-3 and C-5), 50.8 (OCH_3), 127.1 (C-1), 156.0 (C-2), and 166.7 (CO_2R). Hydrolysis in methanolic KOH (see below) gave 2-methyl-1-cyclopentene-1-carboxylic acid (**1**) in 95% yield: mp 129–130 °C (lit.[11] 125 °C).

Reaction of Enol Anisoate 10c with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of lithium dimethylcuprate (20 mmol) was added 2.78 g (10 mmol) of enol anisoate **10c.** The reaction mixture was kept at −20 °C for 2.5 h, quenched with methanol at −20 °C, filtered to remove the copper salt, diluted with water, and extracted with ether. The ethereal extracts were washed (water and brine), dried over $MgSO_4$, and concentrated. The crude product was chromatographed and evaporatively distilled at 55 °C (2 mm) to give 850 mg (60% yield) of ester **11.**

Reaction of Enol Ethylcarbonate 10d with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of lithium dimethylcuprate (20 mmol) was added 2.14 g (10 mmol) of enol ethylcarbonate **10d.** The reaction mixture was kept at − 20 °C for 2.5 h, then quenched with methanol. Isolation as described for reaction with **10c** gave 635 mg (45%) of ester **11.**

Reaction of Enol Mesitoate 10e with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of lithium dimethylcuprate (20 mmol) was added 1.15 g (4 mmol) of enol mesitoate **10e.** The reaction mixture was maintained at −20 °C for 2.5 h, then quenched with methanol. Isolation as described for **10c** gave 200 mg (36% yield) of ester **11.**

Reaction of Enol Pivaloate 10f with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of lithium dimethylcuprate (40 mmol) was added 4.52 g (20 mmol) of enol pivaloate **10f.** The reaction mixture was stirred at that temperature for 30 min, then raised to room temperature and stirred for another 1.5 h. The reaction mixture was quenched with 3 N HCl at −20 °C, and the copper salt was filtered. Isolation as described for reaction with **10c** gave 2.0 g (71% yield) of ester **11.**

Methyl 2-Chloro-1-cyclopentene-1-carboxylate (15). To a cooled (0 °C), stirred suspension of PCl_5 (50 g, 0.24 mol) in 100 mL of anhydrous hexane was added dropwise 14.2 g (0.1 mol) of keto ester **9.** Reaction set in immediately with evolution of hydrogen chloride, and the reaction was completed by refluxing at 60 °C for 2 h, cooling with a dry-ice bath, and adding anhydrous methanol (10 mL). The methanol layer was extracted twice with 50-mL portions of hexane, and the hexane solution was washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated. The residue was distilled at 52 °C (0.5 mm) to give 12.80 g (80%) of chloro ester **15:** IR (film) 1720 (C=O), 1630 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 3.66 (s, 3 H, CO_2CH_3), 1.65–2.84 (m, 6 H).

Reaction of Chloro Ester 15 with Lithium Dimethylcuprate. To a cooled (−78 °C), stirred solution of ethereal lithium dimethylcuprate (60 mmol) was added 6.85 g (42.6 mmol) of β-chloro ester **15** in 15 mL of anhydrous ether. After 1.5 h at −78 °C, the reaction mixture was quenched with 3 N HCl at −30 °C. The copper salt was filtered, and the aqueous layer was extracted twice with 100-mL portions of ether. The combined ethereal solution was washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated. The crude product was chromatographed and distilled at 55 °C (2 mm) to give 5.90 g (greater than 99% yield) of methyl ester **11.**

2-Methyl-1-cyclopentene-1-carboxylic acid (1). Methyl 2-methyl-1-cyclopentene-1-carboxylate (**11**) (800 mg, 5.71 mmol) was added to methanolic potassium hydroxide solution (1.0 g of KOH) at room temperature, and the mixture was refluxed overnight. The residue remaining after concentration was acidified with 3 M H_2SO_4. The liberated acid was extracted three times with 50-mL portions of ether, and the combined ethereal solution was washed (water and brine) and dried over $MgSO_4$. The solvent was removed at reduced pressure to give 750 mg of crude acid as a yellow solid, which upon recrystallization from hexane at 0 °C gave 700 mg (97% yield) of acid **1** as a white solid (mp 129–130 °C; lit.[11] mp 125 °C): ^{13}C NMR δ 16.5 (C-2 CH_3), 21.3 (C-4), 33.3 and 41.1 (C-3 and C-5), 126.8 (C-1), 159.3 (C-2), and 171.9 (C-6).

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Registry No.—1, 67209-77-2; **9,** 10472-24-9; **10a,** 55226-41-0; **10b,** 67209-78-3; **10c,** 67209-79-4; **10d,** 67209-80-7; **10e,** 67209-81-8; **10f,** 67209-82-9; **11,** 25662-30-0; **15,** 66839-38-1; isopropenyl acetate, 108-22-5; benzoyl chloride, 98-88-4; ethyl carbonochloridate, 541-41-3; *p*-methoxybenzoyl chloride, 100-07-2; 2,4,6-trimethylbenzoyl chloride, 938-18-1; 2,2-dimethylpropanoyl chloride, 3282-30-2; lithium dimethylcuprate, 15681-48-8.

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Reduction by Tributyltin Hydride of Carbonyl Compounds Adsorbed on Silica Gel: Selective Reduction of Aldehydes

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Recently, we became interested in photochemically initiated reductions of adsorbed organic substrates by tributyltin hydride and were surprised to observe the rapid and efficient reduction of carbonyl groups adsorbed on dried silica gel, *but in the dark.*[2] This note describes investigations of these reactions and reveals the synthetic utility of tributyltin hydride reductions under these conditions.

Tributyltin hydride is one of the more readily available[3] and least reactive organotin hydrides.[4] In the absence of catalysts it will readily reduce strongly electrophilic species such as carbonium ions,[5] isocyanates,[6] isothiocyanates,[6] and carbonyl groups bearing powerful electron-withdrawing functions.[4] It also reacts spontaneously with alkyl iodides and bromides.[4] If radical initiators are present [e.g., ultraviolet light, azobis(isobutyryl)nitrile], then alkyl chlorides, aryl halides, esters, ketones, and other functional groups can also be reduced,[4,8-10] although elevated temperatures are often required. However, we found that in the presence of a cyclohexane slurry of dried silica gel, tributyltin hydride cleanly reduced aldehydes and ketones to give high yields of the corresponding alcohols (Table I). Sulfoxides, nitro groups, esters, arylnitriles, and alkyl, aryl, and benzylic chlorides were not effectively reduced. Attempted reduction of phenyl benzoate gave some phenol, but a blank reaction in the absence of tributyltin hydride gave the same result, indicating that the product arose from silicolysis of the ester on the silica gel. The fact that the silica gel had been activated to remove water and the failure to isolate any benzoic acid suggest that the phenol is displaced from the ester by hydroxyl end groups on the silica gel to give a benzoylated silica. Diphenylmethyl benzoate was also not reduced, and in this case no evidence for ester dissociation was observed.

Attempted reduction of an epoxide, that of *trans*-stilbene, led to the product of acid-catalyzed opening of the epoxide followed by pinacol rearrangement and reduction of the resulting carbonyl group. This was confirmed by a blank reaction where stilbene epoxide was treated with a cyclohexane slurry of dried silica gel; 2,2-diphenylacetaldehyde was isolated as the only major product.

With the exception of strained ketones such as norcamphor, the rate of reduction of carbonyl groups was found to be in the order aldehydes > dialkyl ketones > aralkyl ketones > diaryl ketones (Table I). When equimolar mixtures of aldehydes and ketones were treated with 1 equiv of tributyltin hydride in the presence of silica gel, selective aldehyde reduction was achieved (Table II).

Relatively few reagents are available for the selective reduction of aldehydes in the presence of ketones; tetrabutylammonium cyanoborohydride,[11] lithium aluminum tri-*tert*-butyloxyhydride,[12] sodium triacetoxyborohydride,[13] lithium di-*n*-butyl-9-borabicyclo[3.3.1]nonane,[14] diisopropylcarbinol on alumina,[15] and samarium diiodide[16] are ones which have been reported. Excluding the last of these reagents, a comparison has shown[15] that while all are capable of reducing an aldehyde in the presence of a *methyl* ketone, only diisopropylcarbinol on alumina has the ability to distinguish between a cyclohexanone and an aliphatic aldehyde. Tributyltin hydride in the presence of dried silica gel is superior to these reagents in its selectivity (Table II). Since this work was

Table I. Reduction of Organic Functional Groups by Excess Tributyltin Hydride on Dried Silica Gel at Room Temperature

substrate	product	isolated yield, %	minimum reaction time, h
norcamphor	norborneol (*exo* + *endo*)	69[a,b]	0.5
3-cholestanone	3-cholestanol (α + β)	89[a,c]	2
methyl naphthyl ketone	1-(β-naphthyl)ethanol	91[a,d]	4
benzophenone	diphenylmethanal	94[a]	6
benzaldehyde	benzyl alcohol	81[a]	1
octanal	1-octanol	90[a]	1
nitrobenzene	aniline	<5[a,e]	24
trans-stilbene epoxide	1,2-diphenylethanol	82[a]	6
phenyl benzoate	phenol	trace[e]	72
diphenylmethyl benzoate		0[e]	24
1-chloro-2-phenylethane		0[e]	48
diphenyl sulfoxide		0[e]	18
benzyl chloride		0[e]	24
phenyl bromide		0[e]	24
benzonitrile		0[e]	24

[a] Average of at least two determinations. [b] 92% endo by VPC (20% Carbowax 20M on Chromosorb W, 100 °C, 7 ft) and ^{1}H NMR assay (average of at least two determinations); reduction with $Bu_3SnH/ZnCl_2/Et_2O$ solution gave 89% endo. [c] 89% β, computed from isolated yields of α and β isomers after separation by TLC and crystallization (average of at least two experiments); reduction with $Bu_3SnH/ZnCl_2/Et_2O$ solution gave 85% β. [d] Reduction with $Bu_3SnH/ZnCl_2/Et_2O$ solution gave a 77% yield of the alcohol. [e] Starting material recovered unchanged.

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Table II. Selective Carbonyl Reduction

carbonyl compounds[a]	% reduction[b]	reducing agent
benzaldehyde	97	tributyltin hydride[c]
methyl naphthyl ketone	8	on silica gel
n-octanal	99	tributyltin hydride[c]
cyclohexanone	13	on silica gel
n-decanal	84[d]	diisopropylcarbinol
4-*tert*-butylcyclohexanone	13[d]	on alumina[d]

[a] An equimolar mixture was used. [b] Determined by VPC and ^{1}H NMR spectroscopy; average of at least two experiments. [c] A slight excess of hydride was used. [d] From ref 15.

completed, two more reports concerning reagents capable of selective reduction of aldehydes have appeared.[17,18]

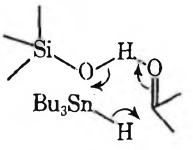
Experiments performed to investigate the mechanism of the reduction indicated that the reactions proceed via a hydride transfer mechanism analogous to complex metal hydride reductions.[19] Thus, the reductions were not inhibited by a radical scourge (2,6-di-*tert*-butylcresol), and only 1 equiv of tributyltin hydride was required, whereas radical-catalyzed tin hydride reductions utilize 2 equiv.[8] Furthermore, no reduction occurred in the presence of methanol or in the absence of silica gel, but it went inefficiently in the presence of dried basic alumina and proceeded well in the presence of zinc chloride. It would appear, therefore, that the function of the silica gel is largely that of a mild acid catalyst and serves to polarize the carbonyl group of the ketone sufficiently to allow reduction by the weakly nucleophilic hydride. This behavior is similar to that of sodium cyanoborohydride[19] and is consistent with the ability of tributyltin hydride to reduce highly electrophilic carbonyl groups without the aid of a catalyst.[7] Reduction in the presence of undried silica gel was not observed, presumably because of the hydrolysis of the tin hydride.

We have also demonstrated that tributyltin hydride does not undergo an exchange with the solid support to produce a "reducing silica gel" in an analogous manner to the formation of the "oxidizing alumina" obtained following treatment with a diacyl peroxide.[20] Treatment of dried silica gel with a cyclohexane solution of tributyltin hydride, filtration under an inert atmosphere, and treatment of the silica gel with a cyclohexane solution of a ketone gave no reduction, while the filtrate did reduce norcamphor if fresh, dried, silica gel was added.

Comparison of the stereochemistry of reduction of tributyltin hydride in the presence of a cyclohexane-dried silica gel slurry, by tributyltin hydride with zinc chloride dissolved in ether (a homogeneous system), and by common complex metal hydrides[21] (see footnotes *b*, *c*, and *d* in Table I) indicates that there is no steric effect upon the reaction due to surface adsorption on the silica gel and that it is apparently only acting as an acid catalyst. Catalysis of tributyltin hydride reduction by zinc chloride has been reported previously[22] but was not fully investigated. Our work shows that in terms of reaction rate it is more efficient than dried silica gel, but it suffers from the disadvantage that an aqueous workup is necessary to remove the zinc chloride and to destroy the zinc salts of the product alcohol, thus resulting in lower isolated yields.

The fate of the tributyltin moiety following carbonyl reduction was also examined. Treatment of a ketone (norcamphor) with approximately 1 equiv of tributyltin hydride in a silica gel–cyclohexane slurry followed by filtration and washing of the silica gel with ether gave the reduced ketone in high yield, but no tin-containing compounds were isolated when the filtrate and washings were evaporated, indicating that the latter were strongly bound to the silica gel. Displacement could not be effected by dry or moist ether or ethanol, but washing with an ethanol–acetic acid mixture allowed the isolation of tributyltin acetate, identical with a prepared authentic sample.

The isolation of tributyltin acetate along with the observations described above are consistent with, but do not require, a six-center reduction mechanism of type A to give



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stannylated silica gel and the alcohol. Alternatively, the initial formation of a tributyltin alkoxide and subsequent exchange with silanol groups may give the same products.

Conclusions

We have demonstrated that silica gel catalyzed reduction of ketones and aldehydes by tributyltin hydride is a selective and high yield method with the advantage of mild nonbasic conditions and without the need of strong acidic workup to neutralize alkoxide salts. Reductions are performed simply and the products easily isolated in the pure state by elution off the silica gel. Most importantly, the method allows the reduction of aldehydes in the presence of ketones with a high degree of selectivity.

Experimental Section

Tributyltin hydride was prepared from tributyltin chloride by reduction with sodium borohydride in glyme.[3] The silica gel used was Baker column chromatography grade, 60–200 mesh, and it was activated by heating at 220 °C at a pressure of less than 1 mmHg for 20 h and stored in a desiccator until required. Cyclohexane was purified by passage through a column of alumina, and zinc chloride was freshly fused. All reactions were carried out under a dry, oxygen-free, nitrogen atmosphere.

General Procedure for Tributyltin Hydride Catalyzed Reduction. The compound to be reduced (1 mmol), silica gel (5 g), tributyltin hydride (1.2 mmol), and cyclohexane (20 mL) were stirred together until TLC indicated that the reaction was complete. The mixture was filtered, and the silica gel was washed first with cyclohexane to remove excess tributyltin hydride and then with ether. The ethereal washings were evaporated to yield the alcohol, which was purified by crystallization, or in the case of liquids by preparative TLC. All reduction products were identified by comparison with authentic samples. The results are given in Table I. In the case of ketones insoluble in cyclohexane, a more polar solvent can be used or the ketone can be preadsorbed onto the silica gel.

General Procedure for Zinc Chloride Catalyzed Reduction. To a freshly filtered, saturated, ethereal solution of zinc chloride (ca. 20 mL) was added the ketone (1 mmol) and tributyltin hydride (1.2 mmol), and the solution was stirred until TLC indicated that the reaction was complete. A white solid was precipitated as the reaction progressed. Following an aqueous workup procedure, the product was purified by crystallization. The results are given in Table I.

Selective Reduction of an Aldehyde in the Presence of a Ketone. Cyclohexanone and octanal or benzaldehyde and *methyl* naphthyl ketone (1 mmol of each) were stirred with tributyltin hydride (1.05 mmol) in cyclohexane (25 mL). Silica gel (10 g) was added, and after 2 h the mixture was filtered. The filtrand was washed with cyclohexane and then with ether, and the latter washings were carefully evaporated to give the product mixture. The relative amounts of cyclohexanone and octanal and their reduction products were determined by VPC (5% Carbowax 20M on Chromosorb P, 80 °C, 6 ft) using a calibration obtained with authentic mixtures. The relative amounts of benzaldehyde and methyl naphthyl ketone and their reduction products were determined from the ^{1}H NMR spectrum of the mixture. The results are given in Table II.

Isolation of Tributyltin Acetate. Norcamphor (2.5 mmol), tributyltin hydride (1 mmol), and silica gel (10 g) were stirred together in cyclohexane for 1 h. The mixture was filtered, and the silica gel was washed with ether to remove norborneol and excess norcamphor and then with acetic acid–ethanol (1:5). Evaporation of the ethanol–acetic

acid washings gave the crude tributyltin acetate, which was recrystallized from petroleum ether (bp 60–80 °C) to give the pure product (79%), mp 84–85 °C, identical (mixed melting point and IR) with a prepared authentic sample.[23]

Registry No.—Norcamphor, 497-38-1; 3-cholestanone, 15600-08-5; methyl naphthyl ketone, 93-08-3; benzophenone, 119-61-9; benzaldehyde, 100-52-7; octanal, 124-13-0; nitrobenzene, 98-95-3; *trans*-stilbene epoxide, 1439-07-2; phenyl benzoate, 93-99-2; diphenylmethyl benzoate, 7515-28-8; 1-chloro-2-phenylethane, 622-24-2; diphenyl sulfoxide, 945-51-7; benzyl chloride, 100-44-7; phenyl bromide, 108-86-1; benzonitrile, 100-47-0; 1-(β-naphthyl)ethanol, 7228-47-9; diphenylmethanol, 91-01-0; benzyl alcohol, 100-51-6; 1-octanol, 111-87-5; aniline, 62-53-3; 1,2-diphenylethanol, 614-29-9; phenol, 108-95-2; cyclohexanone, 108-94-1; *n*-decanal, 112-31-2; 4-*tert*-butylcylohexanone, 98-53-3; tributyltin hydride, 688-73-3; tributyltin acetate, 56-36-0; *exo*-norborneol, 497-37-0; *endo*-norborneol, 497-36-9; 3α-cholestanol, 516-95-0; 3β-cholestanol, 80-97-7.

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Improved Routes to Phenalene and Phenalanone. Alane, Borane, and Silane Reductions of Phenalenone

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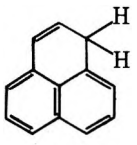
Phenalene (1) has enjoyed considerable attention from chemists because of its ability to generate an anion, neutral radical, and cation, all of which are aromatic and stable in solution.[1] Because earlier reported methods of making and isolating 1 and its precursors are generally tedious[2] and work



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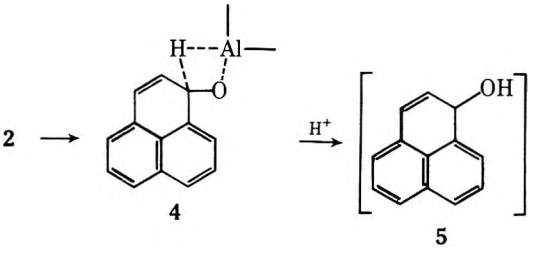
in our laboratories required ready access to **1**, we investigated ways of improving its yield and purification.

Recently, it was reported that $LiAlH_4/AlCl_3$ reduced phenalenone (**2**) to **1** and phenalanone (**3**).[3] The yields varied over a wide range, however, and were markedly affected by the purity of the $LiAlH_4$ and $AlCl_3$, the recommended procedure calling for newly opened bottles of these reagents. Furthermore, the isolation of **1** required large amounts of solvent and is often accompanied by oxidation of the very sensitive **1** on silica gel.

The active agents in the reduction of **2** to **1** by the $LiAlH_4/AlCl_3$ mixture were probably $HAlCl_2$ and H_2AlCl.[4] This suggested to us that diisobutylaluminum hydride (DIBAL-H) might also be effective in reducing **2**. We found that DIBAL-H will convert **2** to **1** in high net yields (>85%) and that **1** can be isolated easily in high purity from the product mixture. DIBAL-H is commerically available as a 1 M solution in hexane (Aldrich) and is handled conveniently and precisely by syringe technique. The reagent also has a long shelf-life, even after it has been sampled. These are distinct advantages over $LiAlH_4/AlCl_3$ mixtures.

The sensitivity of **1** to silica gel led us to try other solid supports, and we found that Florisil, a much more acidic absorbent than silica gel,[5] gave very satisfactory results. Phenalene is the first compound eluted from the column and is well separated from the only other product, phenalenone. Moreover, a shorter column and much less solvent are required than when we used silica gel. No significant decomposition of **1** during the chromatography was observed. Scaling up the reaction presented no handling problems, and yields were unchanged.

The production of **1** from **2** and DIBAL-H probably arises from a 1,2 addition of the metal hydride across the C=O bond. Hydrolysis of the resulting alkoxide would give phenalenol **5**, which is known to undergo a facile irreversible disproportionation to **1** and **2**.[6] Consistent with this scheme is the fact that we recover ~50% of the amount of **2** that we start with regardless of reaction time and the number of equivalents of DIBAL-H used. Reaction times ranged from 4 h to 2 days, and ratios of metal hydride to **2** were varied from 1 to 5 equiv. The addition of aluminum powder or aluminum chloride as potential deoxygenating agents did not change the yield of **1**.



→ 1 + 2

We tried to intercept the disproportionation of **5** by using alcohols in large excess during workup. However, allyl alcohol, glyoxal, and benzoin did not alter the yield or product distribution. The report of successful hydrogenolysis of the magnesium alkoxides of allylic alcohols using complexes derived from adding *n*-propylmagnesium bromide[7] to bis(phosphine)nickel dichlorides suggested that **4** might be similarly reduced. This route also gave **1** and **2** when applied to **4**. We also tried reductions of **2** using boranes and found that while BH_3-SMe_2 is useful for preparing cyclopropane from cyclopropenone,[8] mainly polymeric products are obtained when it is used with **2**. 9-Borabicyclononane, on the other hand, does give **1** in net yields of ~90% when stirred overnight at room temperature in THF.

We extended our studies to polymethylhydrosiloxane (PMHS)[9] and tetramethyldisiloxane (TMDS)[9] and found that

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the major product was phenalanone (3). While small amounts of 3 can be obtained from the $LiAlH_4/AlCl_3$ reduction of 2,[3] the best known synthesis is the cyclization of β-1-napthylpropionic acid using anhydrous hydrogen fluoride.[2] The latter route is inconvenient and limited to small scale reactions because of the precautions necessary when using anhydrous HF. This cyclization procedure also gives the isomeric mixture, phenalanone/4,5-benzhydrindone.

We have prepared 3 in ~30% yield using 2 equiv of TMDS and 2 in acidified 95% ethanol in the presence of catalytic amounts of palladium. Although the yield is modest, the simple reaction conditions, ready availability of these inexpensive reagents and ease of product isolation make this an attractive synthesis of 3. PMHS was found to be less effective than TMDS, giving yields of ~20%. No improvement in this yield was observed over the range of 1.1 to 4.4 equiv[9] of PMHS to 2.

Experimental Section

Phenalenone was prepared by the method of Fieser and Hershberg.[10] Benzene and hexane were stirred over H_2SO_4, distilled, and stored in brown bottles until needed. Tetrahydrofuran was refluxed over sodium metal and benzophenone until the blue color of benzophenone ketyl was observed, and then it was distilled just before use. NMR spectra were recorded on a Varian EM-390 spectrometer and correspond to those reported in the literature.[11] Melting points were obtained on a Thomas-Hoover Mel-Temp melting point apparatus and are uncorrected. All glassware was oven-dried, assembled hot, and cooled under a stream of dry nitrogen. The reactions were run under a dry nitrogen atmosphere unless otherwise noted. Florisil was placed in a round-bottom flask, put under vacuum, and purged with N_2. This cycle was repeated several times just before use.

DIBAL-H Reduction of Phenalenone. Excess DIBAL-H (11.2 mL, 1 M in hexane; Aldrich Chemical Co.) was added to a benzene solution (~20 mL) of 2 (1.0 g, 5.5 mmol) over a 30-min period at room temperature. The resulting dark red solution was heated to reflux overnight and cooled to room temperature, and excess DIBAL-H was quenched by the dropwise additon of 2 mL of a saturated NH_4Cl solution. Hexane (50 mL) was added and the mixture filtered. The salts were washed with 1 × 50 mL of hexane. The hexane layers were combined, washed with 1 × 50 mL of the NH_4Cl solution, and dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The oil was deposited on Florisil (100–200 mesh; Matheson, Coleman and Bell) and placed atop a 10 × 5 cm column of Florisil. Elution was with 250 mL of hexane; 50-mL fractions were collected. Fractions 2–4 contained 1 (0.40 g, 2.41 mmol), mp 70–75 °C (lit. mp 85 °C).[2] The column was then eluted with 50 mL of 1:1 hexane/ether, and 2 (0.52 g, 2.88 mmol) was recovered. The isolation of 2 from the product mixture was confirmed by comparison of its melting point and IR and NMR spectra with those of an authentic sample.

9-Borabicyclononane (9-BBN) Reduction of Phenalenone. Excess 9-BBN (6 mL, 0.5 M in THF; Aldrich Chemical Co.) was added slowly to a THF solution (~15 mL) of 2 (0.50 g, 2.8 mmol) at 0 °C. The solution was stirred overnight at room temperature. Excess 9-BBN was quenched with 0.5 mL of methanol.[12] NaOH (3 M, 1 mL) and 2 mL of 30% H_2O_2 were added, and the mixture was heated to reflux for 1 h. Anhydrous K_2CO_3 was added to saturate the aqueous phase; the organic layer was decanted, and the K_2CO_3 was extracted with 3 × 20 mL of ether. The organic layers were combined, washed with 4 × 30 mL of H_2O, and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the oil was deposited on Florisil. This was placed atop a 10 × 2 cm Florisil column. Elution was with 100 mL of hexane. This fraction contained 1 (0.20 g, 1.20 mmol) as pale yellow crystals, mp 65–75 °C. The column was then eluted with 50 mL of 1:1 hexane/ether, and crude 2 (0.26 g, 1.4 mmol, 52%) was obtained.

Purification of Phenalene. Analysis of the chromatographed samples of 1 from the above reductions by NMR spectroscopy showed that the impurities were saturated hydrocarbon residues. However, if 1 must be further purified, the following procedure[13] is recommended.

1 was dissolved in sufficient pentane (~6 mL/g) so that when the resulting solution was chilled to dry ice temperature, a filterable slurry was formed. During the chilling period (~30 min), a Büchner funnel wrapped in aluminum foil and a stoppered flask containing pure solvent were chilled in powdered dry ice. Immediately before use, a conventional filtration assembly was set up using the chilled funnel. The slurry of 1 was filtered and washed with the chilled solvent. An inverted funnel connected to a dry N_2 source was placed over the Büchner funnel, and suction was continued until the apparatus reached room temperature. Phenalene was obtained as a white powder (mp 83–84 °C), and no hydrocarbon residue was visible in the NMR spectrum. The structure was confirmed by comparison of its NMR spectrum [(in $CDCl_3$) δ 2.5–4.1 (m, 8 H), 6.1 (s, 2 H)] with published data.[11]

We have carried out this procedure many times, including runs on as much as 5 g of 2, and in all cases the net yields of 1 exceeded 80% based on recovered 2.

TMDS Reduction of Phenalenone. Palladium on charcoal (5%) (10 mg; Matheson, Coleman and Bell) and a few drops of 12 M HCl were added to a solution of 2 (5.0 g, 27.7 mmol) in 95% ethanol, and the mixture was heated to reflux. TMDS (11.1 mL, 62.3 mmol) was added by syringe through the condenser at a rate to maintain the reflux, which was continued for 1 h after the addition was complete. The mixture was filtered, and the volatile products were removed by rotary evaporation to give ~3 mL of an orange-brown oil. This was dissolved in 50 mL of ether and washed with 3 × 50 mL of H_2O. The H_2O layers were combined and washed with 1 × 50 mL of ether. The ether layers were combined, washed with 1 × 50 mL of a saturated NaCl solution, dried (Na_2SO_4), and filtered, and the ether was removed by rotary evaporation. The residual oil was deposited on alumina (neutral, Alcoa F-20) and placed atop a 25 × 5 cm column of alumina. The product was eluted with 1:1 hexane/ether; 100-mL fractions were collected. Fractions 4 and 5 contained 3 (1.4 g, 7.9 mmol, 28%), mp 80–81 °C (lit.[2] mp 82.6–83.2 °C). No phenalenone was detected in the product mixture. The structure of 3 was confirmed by its NMR [(in $CDCl_3$) δ 1.9–2.7 (m, 6 H), 6.5–7.2 (m, 4 H)] and IR [(in CCl_4) 1700 cm^{-1} (C=O)] spectra, which compare well with the published spectra.[11]

Acknowledgment. Financial support from the Research Corporation is gratefully acknowledged.

Registry No.—1, 203-80-5; 2, 548-39-0; 3, 518-85-4.

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Studies with Amino Acids. 1. Synthesis of Valine

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The synthesis of amino acids by the Strecker[1] method is well known and offers one of the best routes available for the preparation of these important compounds. Several modifications have been introduced which increase the yields and safety of the preparation. The method has been of great value in the preparation of carboxyl-labeled amino acids starting with ^{13}C and ^{14}C cyanide, but difficulties arise when synthesizing amino acids labeled with ^{11}C. Compounds labeled with this isotope have great potential for in vivo metabolism studies using nuclear medicine techniques. The short half-life of ^{11}C (20 min) requires considerable modification in existing procedures. The method presented here proceeds smoothly and rapidly without the production of any interfering byproducts. The procedure is described for the synthesis of valine (Scheme I), but may be used for the preparation of other amino acids.

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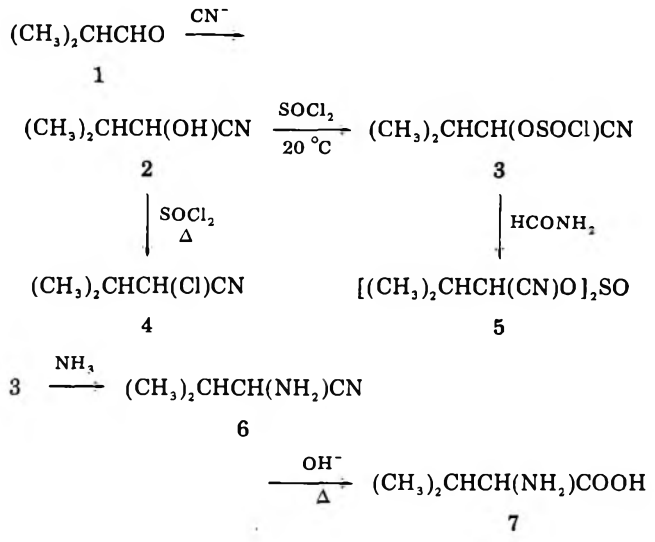
Scheme I



The preparation of the cyanohydrin **2** was carried out using anhydrous ether as solvent, although no special precautions were used to exclude traces of water. Under these conditions the aldehyde is quantitatively converted to a colorless product of very high purity. It distills without decomposition at 0.1-mm pressure. Water is undoubtedly involved in the reaction, but only trace amounts seem necessary to drive it forward. The potassium cyanide contains some moisture, leading to the reaction:

$$CN^- + H_2O = HCN + OH^-$$

$$OH^- + HAc = Ac^- + H_2O$$

Under the conditions described the acetate ion is removed as KAc and the reaction goes to completion. The presence of 1 molar equiv of water did not affect the yield, but the formed potassium acetate became heavy and pasty, making stirring difficult. A large volume of ether facilitates stirring and isolation of the product. The IR spectra of the cyanohydrin before and after distillation were identical, showing a weak band at 2260 cm^{-1} (CN), a broad intense band at 3440 cm^{-1} (OH), and an intense, rather broad band at 1056 cm^{-1} (OH deformation vibrations).

In the preparation of the chlorosulfinyl nitrile **3** from **2** it is desirable that the latter be anhydrous even though water has little effect on the yield if an excess of thionyl chloride is used. In a rapid but smooth reaction **2** is converted to **3** in over 90% of theory. Upon fractionation the product is obtained as a colorless oil. The IR spectra indicates that the presence of the sulfinyl group suppresses considerably the nitrile band at 2260 cm^{-1}, although it is still detectable. A very intense rather broad band appears at 1213 cm^{-1} (SO), indicating a shift to a higher frequency due to the presence of additional oxygen attached to the SO group.

In addition to the formation of **3** by the action of thionyl chloride on **2** two other compounds are formed. The residue remaining after the distillation of **3** from the reaction mixture consists almost entirely of **5**, the sulfite. It distills without decomposition at 0.1 mm, but cannot be freed from a trace of color even by repeated distillations of an analytically pure sample. On the other hand, a colorless sample can be prepared by treating **3** with an excess of formamide and washing the ether-extracted oil several times with water, drying, and distilling. Microanalysis and IR indicate that both products are of the same compound. Here, too, the nitrile band is present (2260 cm^{-1}), but greatly suppressed. The characteristic band (SO) at 1213 cm^{-1} is intense and rather broad. This sulfite may be reconverted to **3** by refluxing with $SOCl_2$ for 5–10 min.

The third compound formed by the action of $SOCl_2$ on **2** is the chloronitrile **4**. The latter is formed quantitatively from **2** by refluxing the reaction mixture 4–5 h. After the removal of excess $SOCl_2$ it is distilled at atmospheric pressure. For a sample free of sulfur the oil was dissolved in ether and the solution was washed with water until free of chloride. On drying and removal of solvent a sulfur-free product was obtained. The infrared spectrum of this compound shows a band at 2260 cm^{-1} (CN) which is somewhat less intense than the same band in the cyanohydrin. In addition to this, another band appears at 2230 cm^{-1} which is sharper and about three times as intense as that at 2260 cm^{-1}. This band persists after several distillations. There is also a very weak band at 1213 cm^{-1} which still appears after the sulfur content of the sample has been reduced to <0.02%. This band is absent in the cyanohydrin, although the latter does show a weak band at 1247 cm^{-1}. The band at 3440 cm^{-1} (OH) is absent.

The chlorosulfinyl nitrile **3** is rapidly converted to the amino nitrile **6** by the action of liquid ammonia.[2] On removal of excess ammonia the residue is converted to valine (**7**) by refluxing with sodium hydroxide.[3] Hydrochloric acid may be used in this hydrolysis, but base is preferred for this amino acid since there is no apparent tar formation and a chromatographically pure sample is obtained.

Experimental Section

Isobutyraldehyde was purified by distillation just before use. A purified grade of thionyl chloride was further purified by distillation from about 10% of its weight of boiled linseed oil. A colorless product is thus obtained. The ammonia was dried by distillation from a small quantity of clean sodium. All other materials were reagent grade. All boiling points are uncorrected. Analyses are by V. Tashinian Micro Lab, U. C. Berkeley. The infrared spectra were determined on a Perkin Elmer IR 421 (liquid film between KBr plates). The preparation should be carried out in a good fume hood.

2-Hydroxyisovaleronitrile (2). A well stirred suspension of 50 g of potassium cyanide in 800 mL of anhydrous ether was cooled in an ice–water bath and 36.5 g of isobutyraldehyde (1) in 45 mL of glacial acetic acid was added dropwise during 1 h. A light voluminous precipitate of potassium acetate began to form immediately, which eventually filled the whole volume. After stirring for another hour the acetate was removed by filtration and the filter cake was washed several times with small portions of anhydrous ether. The ether was removed from the combined filtrate and washings using a rotary evaporator at room temperature and reduced pressure. The remaining oil weighed approximately 50 g. It distilled without decomposition at 66–67 °C (0.1 mm).

Anal. Calcd for C_5H_9ON: C, 60.60; H, 9.09; N, 14.14. Found: C, 60.62; H, 9.04; N, 14.12.

2-Chlorosulfinyloxyisovaleronitrile (3). The cyanohydrin from the above preparation (50 g) was added to 118 g of thionyl chloride over a period of 30 min while the mixture was stirred and kept at room temperature by means of a water bath. When the evolution of HCl had ceased, the excess thionyl chloride was removed under reduced pressure and the residue was fractionated, yielding almost colorless oil, bp 40–41 °C (0.1 mm).

Anal. Calcd for $C_5H_8O_2NSCl$: C, 33.06; H, 4.40, S, 17.63; Cl, 19.53; N, 7.71. Found: C, 33.36; H, 4.48; S, 17.56; Cl, 19.51; N, 7.70.

The yield for a number of runs varied between 80 and 86 g. The residue which remained was distilled and consisted almost entirely of the higher boiling sulfite **5**, bp 97–98 °C (0.1 mm).

Anal. Calcd for $C_{10}H_{16}O_3N_2S$: C, 49.18; H, 6.56; N, 11.47; S, 13.11. Found: C, 49.52; H, 6.63; N, 11.61; S, 12.86.

2-Chloroisovaleronitrile (4). The chlorosulfinyl nitrile **3** (50 g) as prepared above was refluxed with 60 g of thionyl chloride for 5 h, after which the excess thionyl chloride was removed at atmospheric pressure. The residue distilled at 149–150 °C at atmospheric pressure. The colorless oil weighed 30 g.

Anal. Calcd for C_5H_8NCl: C, 51.08; H, 6.81; N, 11.91; Cl, 30.18. Found: C, 51.31; H, 6.85; N, 12.15; Cl, 29.86.

Isobutyronitrile Sulfite (5). The chlorosulfinyl nitrile **3** (30 g) was added to 30 mL of formamide and the mixture was shaken for several minutes until the exothermic reaction was complete. The mixture was poured into water (100 mL) and the oil was extracted with ether. The ether solution was washed twice with two 20-mL portions of water and dried over anhydrous sodium sulfate. Upon removal of ether and

distillation of the residue there was obtained 18 g of a colorless oil, bp 97–98 °C (0.1 mm).

Anal. Calcd for $C_{10}H_{16}O_3N_2S$: C, 49.18; H, 6.56; N, 11.47; S, 13.11. Found: C, 49.09, H, 6.62; N, 11.59; S, 13.15.

Valine (7). To approximately 35 mL of anhydrous ammonia cooled in a dry ice–acetone bath was added dropwise 18 g of **3**. A vigorous reaction occurs and when complete, the cooling bath was removed and the ammonia was allowed to evaporate. To the residue was added 75 mL of absolute ethyl alcohol and the mixture was heated to reflux. On cooling, 20 g of NaOH in 100 mL of water was added and the temperature increased to above 90 °C, allowing the alcohol to distill off. The mixture was refluxed for 24 h. After cooling, 100 mL of 6 N HCl was added and the mixture was taken to dryness under reduced pressure. A few milliliters of water was added to the residue and it was again taken to dryness. The residue was extracted several times with a total of 200 mL of hot absolute ethyl alcohol. The alcoholic solution was concentrated to approximately 50 mL, filtered, and treated with 15 mL of pyridine. After standing in the refrigerator overnight the crystals were collected, washed with alcohol, and air dried. The yield for several runs was from 8 to 9 g of very pure, almost colorless valine. Paper chromatography showed the sample to be homogeneous, having the same R_f value as a standard sample of valine (1-butanol/acetic acid/water/pyridine; 10:2:2:1).

Anal. Calcd for $C_5H_{11}O_2N$: C, 51.28; H, 9.4; N, 11.96. Found: C, 50.90: H, 8.96; N, 11.99.

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Registry No.—**1**, 78-84-2; **2**, 67226-50-0; **3**, 67226-51-1; **4**, 67226-52-2; **5**, 67226-53-3; **6**, 67226-54-4; **7**, 516-06-3.

References and Notes

(1) See J. R. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol. 1, Wiley, New York, N.Y., 1961, p 698; *ibid.*, Vol. 3, pp 2371–2375.
(2) This amino nitrile has been prepared directly from **2** by the action of ammonia at high temperature and pressure. We carried out the reaction using liquid ammonia at atmospheric pressure, but no amino nitrile could be isolated. However, on a micro scale after hydrolysis some valine could be detected by paper chromatography: see W. T. Gresham and C. E. Schwertzer, U.S. Patent 2 520 312 (1950); *Chem. Abstr.*, **44**, 10732g (1950).
(3) The hydrolysis rate may be increased by increasing the temperature and pressure with no change in the purity of the final product: see ref 1, p 2372.

α-Diazo-β-oxycarboxylates

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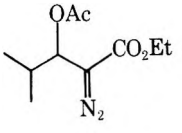
The aldol condensation of α-diazoacetic esters or α-diazomethyl ketones with aldehydes or ketones has been shown to be a facile method of synthesis of α-diazo-β-hydroxycarbonyl compounds,[1] whose pyrolysis has led to β-dicarbonyl substances. In order to study the effect of modification of the hydroxy group and introduction of a neighboring double bond, the following four α-diazo-β-oxy esters were prepared and their pyrolyses were investigated.



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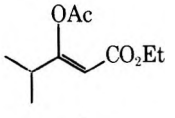
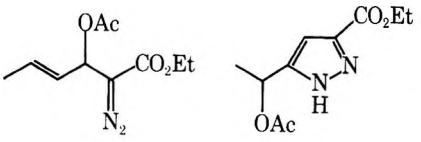


2

Treatment of a tetrahydrofuran solution of isobutyraldehyde and ethyl diazoacetate with *n*-butyllithium at −78 °C and interaction of the resultant lithio salt of the α-diazo-β-hydroxy ester with acetic anhydride yielded ester **1**, whose thermal decomposition gave the enol acetate of ethyl β-oxoisocaproate (**2**). This experience lays the groundwork for a simple, three-step method of preparation of unique enol esters of unsymmetrical β-diketones.

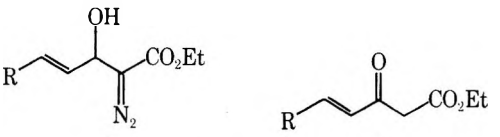
The presence of a double bond vicinal to the acyloxylated carbon causes the pyrolysis to take a different path. Thus, whereas the condensation of crotonaldehyde with diazoacetic ester and subsequent acetylation led to the expected diester **3**, its thermolysis afforded pyrazole **4**. Presumably, ester **3** had



3 4 5

experienced an allyl acetate rearrangement and the resultant isomer (**5**) had undergone the known transformation of vinyl diazo compounds into pyrazoles.[2]

Interaction of ethyl lithiodiazoacetate with acrolein and with crotonaldehyde yielded esters **6a** and **6b**, respectively, whose pyrolysis resulted in the formation of β-keto esters **7a**[3] and **7b**,[3c] respectively. This two-step reaction scheme constitutes the shortest, presently known method of preparation of vinyl keto ester annelating agents, such as the Nazarov reagent **7a**. Their use in natural products synthesis is already on record.[3e,4,5]



6 7

a, R = H
b, R = Me

Experimental Section

Infrared spectra of neat liquids were measured on a Perkin-Elmer 137 spectrophotometer and ^1H NMR spectra of deuteriochloroform solutions on a Varian EM-390 spectrometer.

General Procedure for the Preparation of Diazoesters 1, 3, and 6. The aldehyde and ethyl diazoacetate (in 87% methylene chloride solution), 20 mmol each, were added separately to 50 mL of anhydrous tetrahydrofuran, kept constantly at −78 °C. A 2.4 M hexane solution of *n*-butyllithium, 20 mmol, was added dropwise over a period of 45 min to the stirring, yellow solution under nitrogen at −78 °C and the mixture was stirred for 30 min more at the same temperature. Thereafter 2 mL of acetic anhydride in 50 mL of dry ether (for the preparation of 1 or 3) or 2 mL of glacial acetic acid in 50 mL of anhydrous ether (for the preparation of 6) was added at one time to the stirring solution and the resultant yellow suspension was stirred at room temperature for 1 h. The mixture was washed four times with 20 mL each of saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated under vacuum at room temperature. (Increase of the temperature of the reaction and workup decreased the product yields and led to oils with colors deeper than the yellow color characteristic of α-diazocarbonyl compounds!)

The above procedure used on isobutyraldehyde and ethyl diazoacetate, followed by acetylation, gave 3.9 g of crude diester **1**, which was used in the next reaction without purification. Chromatography of the substance on 200 g of neutral alumina (activity III) and elution with hexane yielded 1.3 g of **1**: IR 4.76 (s, N_2), 5.76, 5.89 (s, C=O) μm; ^1H NMR δ 0.96 (d, 3, J = 6 Hz, Me), 0.99 (d, 3, J = 6 Hz, Me), 1.23 (t, 3, J = 7 Hz, Me of Et), 1.7–2.5 (m, 1, CH), 2.03 (s, 3, Me of Ac), 4.20 (q, 2, J = 7 Hz, CH_2), 5.23 (d, 1, J = 9 Hz, OCH). Anal. Calcd for

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$C_{10}H_{16}O_4N_2$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.89; H, 7.16; N, 12.25.

The procedure applied to crotonaldehyde and ethyl diazoacetate, followed by acetylation, produced 4.1 g of oil, the rapid filtration of whose 9:1 hexane–ethyl acetate solution through 200 g of neutral alumina (activity III) yielded 2.1 g of yellow, liquid ester **3**: IR 4.75 (s, N_2), 5.75, 5.88 (s, C=O) μm; ^{1}H NMR δ 1.26 (t, 3, J = 7 Hz, Me of Et), 1.30 (d, 3, J = 7 Hz, Me), 2.06 (s, 3, Me of Ac), 4.20 (q, 2, J = 7 Hz, CH_2), 5.33 (dd, 1, J = 14, 7 Hz, δ-H), 5.43 (s, 1, OCH), 6.00 (d, 1, J = 14 Hz, γ-H).

Use of the procedure on acrolein and ethyl diazoacetate afforded 4.5 g of oil whose alumina filtration as in the case of ester **3** above led to 1.2 g of yellow, liquid hydroxy ester **6a**: IR 3.00 (m, OH), 4.80 (s, N_2), 5.94 (s, C=O) μm; ^{1}H NMR δ 1.23 (t, 3, J = 7 Hz, Me), 4.20 (q, 2, J = 7 Hz, OCH_2), 5.20 (s, 1, OCH), 5.3–6.1 (m, 3, CH, CH_2).

When the procedure was applied to crotonaldehyde and ethyl diazoacetate, it yielded 3.7 g of an oil whose alumina chromatography, following the above route for ester **3**, gave 2.4 g of yellow, liquid hydroxy ester **6b**: IR 2.98 (m, OH), 4.80 (s, N_2), 5.93 (s, C=O) μm; ^{1}H NMR δ 1.26 (t, 3, J = 7 Hz, Me of Et), 1.73 (d, 3, J = 6 Hz, Me), 4.20 (q, 2, J = 7 Hz, CH_2), 5.23 (s, 1, OCH), 5.4–6.1 (m, 2, $(CH)_2$).

General Procedure for Pyrolysis. All pyrolyses were carried out by passage of neat diazo esters down a vertical, 25-cm long 2-cm i.d. glass tube, filled with glass helices and kept at 280 °C under 0.25 Torr pressure, and the products were trapped in a receiver cooled by dry ice. (Pyrolyses of cyclohexane solutions or pyrolyses of the neat diazo esters at atmospheric pressure yielded substances of different structures than those below.)

The thermolysis of crude diester **1** yielded an oil whose distillation [at 70–75 °C (0.25 Torr)] produced 1.06 g of liquid, air-sensitive ester **2** (27% overall yield for the two reactions): IR 5.68, 5.86 (s, C=O), 6.10 (s, C=C) μm; ^{1}H NMR δ 1.06 (d, 6, J = 7 Hz, Me_2), 1.23 (t, 3, J = 7 Hz, Me of Et), 2.20 (s, 3, Me of Ac), 2.43 (pentet, 1, J = 7 Hz, CH), 4.06 (q, 2, J = 7 Hz, CH_2), 5.53 (s, 1, olefinic H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.05; H, 8.14.

After pyrolysis of pure diester **3** the heating chamber was washed with ethyl acetate and the washings were evaporated. Chromatography of the residue, 1.68 g, on 100 g of neutral alumina (activity III) and elution with 9:1 hexane–ethyl acetate yielded 0.31 g of unidentified material and then 1.05 g of viscous liquid pyrazole **4** (23% overall yield): IR 2.89 (w, NH), 5.82, 5.89 (s, C=O), 6.31 (m, C=C) μm; ^{1}H NMR δ 1.33 (t, 3, J = 7 Hz, Me of Et), 1.60 (d, 3, J = 6 Hz, Me), 2.06 (s, 3, Me of Ac), 4.33 (q, 2, J = 7 Hz, CH_2), 5.96 (q, 1, J = 6 Hz, OCH), 6.76 (s, 1, CH).

Pyrolysis of pure hydroxy ester **6a** yielded 0.55 g of keto ester **7a** (20% overall yield); IR and ^{1}H NMR spectra were identical with those reported earlier.[3c]

Pyrolysis of pure hydroxy ester **6b** and subsequent heating of the pyrolysate at 60 °C (30 Torr) for the removal of volatile, unidentified material gave 1.6 g of liquid keto ester **7b** (53% overall yield); IR and ^{1}H NMR spectra were identical with those quoted earlier.[3c]

Acknowledgment. The authors express their gratitude to the Squibb Institute for Medical Research for support of this work.

Registry No.—**1**, 67272-01-9; **2**, 67272-02-0; **3**, 67272-03-1; **4**, 67272-04-2; **6a**, 67272-05-3; **6b**, 67272-06-4; **7a**, 22418-80-0; **7b**, 17544-47-7; isobutyraldehyde, 78-84-2; ethyl diazoacetate, 623-73-4; crotonaldehyde, 4170-30-3; acrolein, 107-02-8.

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(2) Cf. C. D. Hurd and S. C. Liu, *J. Am. Chem. Soc.*, **57**, 2656 (1935); J. Marx and L. Marx-Moll, *Chem. Ber.*, **87**, 1499 (1954).

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(5) **Note Added in Proof:** An alternate short synthesis of esters of type **7** is described by P. Pollet and S. Gelin, *Synthesis*, 142 (1978).

Oxidation of Substituted Hydroquinone Monoalkyl Ethers to *p*-Benzoquinone Monoketals

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Received April 20, 1978

Blocked benzoquinones are potentially attractive intermediates in synthesis, but until recently no widely applicable methods were known for their preparation. Cyanotrimethylsilyloxycyclohexadienones[2,3,4] and *p*-benzoquinone ketals have received most of the attention. Olefination of the latter class of compounds produced protected quinone methides,[5] and other transformations led to polycyclic biaryls.[6] Carbonium ions derived from *p*-quinone monoketals by carbon–oxygen heterolysis were found to undergo [2 + 4] cycloadditions with olefins.[7] The resulting adducts were easily transformed to neolignans[8] of the bicyclo[3.2.1]octane, hydrobenzofuran, and spiro[5.5]undecane types.

In the past, quinone ketals were prepared sporadically, usually in low yields, by the oxidation of 4-alkoxy- or 4-aryloxyphenols in alcohol with copper(II) species, ceric salts, silver oxide, manganese dioxide, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[9] Consequently, these reagents were used only rarely until McKillop and Taylor described their preparation using thallium(III) nitrate as the oxidant.[10]

We have prepared a number of *p*-quinone ketals by this procedure (see Table I) and noticed that the yield of the acid-sensitive products could be increased by performing the oxidations in the presence of suspended potassium bicarbonate (see Experimental Section). To replace the toxic thallium salt and also because ketals **9** and **15** were not available by this method, other oxidants were examined. Of those tried, DDQ and ferric chloride proved to be most satisfactory. To suppress acid-catalyzed transformations of the resulting ketals, it is advisable to perform the oxidations with ferric chloride in the presence of potassium carbonate. Some of the more highly oxygenated ketals display significant water solubility, and the yields given in Table I could undoubtedly be improved if continuous extraction was used in the workup procedure.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are corrected. Proton magnetic resonance (^{1}H NMR) spectra (90 MHz) were recorded on a Perkin-Elmer R-22 spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT 44 instrument. Ultraviolet (UV) spectra were obtained on a Perkin-Elmer 202 spectrometer. Infrared (IR) spectra were taken with a Perkin-Elmer 247 or 237B grating spectrometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

Physical Properties of the New *p*-Quinone Ketals. 2-Allyl-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (4): mp 49–50 °C (ether–pentane); IR ($CHCl_3$) 1690, 1655, 1630 cm^{-1}; NMR (CCl_4) δ 3.09 (br d, 2, J = 7 Hz, C=CCH$_2$), 3.26 (s, 3, –OCH$_3$), 4.98–5.26 (m, 2, CH$_2$=C), 5.49 (s, 1, –OCH$_2$O–), 5.55 (s, 1, –OCH$_2$O–), 5.60 (s, 1, CO—CH=C), 5.70–6.10 (m, 1, C=CH), 6.53 (t, 1, J = 1 Hz, C=CH); UV (95% EtOH) 237 nm (ϵ 9350), 295 (3200); mass spectrum (70 eV), *m/e* (relative intensity) 208 (M^+, 13), 69 (100); ^{13}C NMR ($CDCl_3$) δ 32.6 (t of m), 51.2 (q), 97.6 (br), 98.9 (d), 98.9 (t), 117.9 (t of m), 127.8 (d of t), 134.4 (d of m), 142.8 (br), 168.3 (s), 186.8 (s). Exact mass calcd for $C_{11}H_{12}O_4$: 208.07356. Found: 208.07275.

2-Allyl-4-(2-chloroethoxy)-4,5-methylenedioxycyclohexa-2,5-dienone (5): mp 105–106 °C (ether–pentane); IR ($CHCl_3$) 1690, 1655, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (br d, 2, J = 7 Hz, C=CCH$_2$), 3.53–3.92 (m, 4, –OCH$_2$CH$_2$Cl), 5.04–5.32 (m, 2, CH$_2$=C), 5.66 (s, 1, –OCH$_2$O–), 5.68 (s, 1, –OCH$_2$O–), 5.82 (s, 1, CO—CH=), 5.73–6.13

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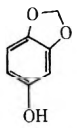
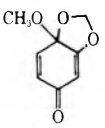
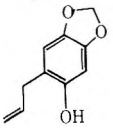
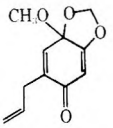
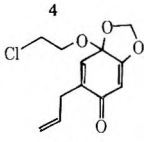
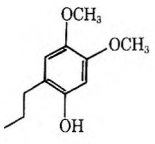
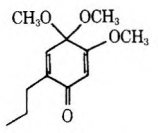
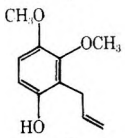
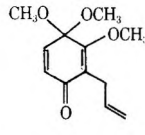
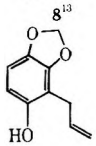
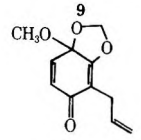
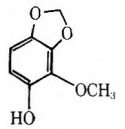
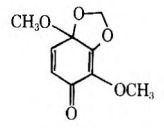
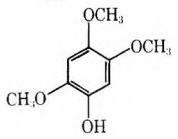
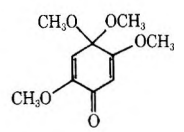
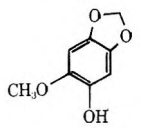
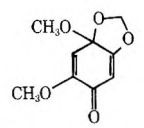
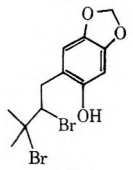
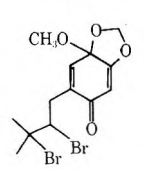
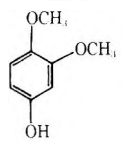
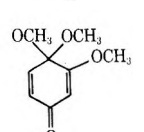
Table I

phenol	quinone ketal	yield, % DDQ	$FeCl_3$	$Tl(NO_3)_3$
 1	 2	<5	<5	83[a]
 3	 4	88	84	78
	 5[11]	63		
 6[12]	 7	85	88	80
 8[13]	 9	75	0	0
 10[14]	 11	31	0	21
 12[15]	 13	57	0	68
 14[16]	 15	<5	78	0
 16[17]	 17	50	50	70
 18[18]	 19	97		
 20[16]	 21[6]	<5	<5	66

[a] Reference 10, 45%.

(m, 1, C=CH), 6.72 (t, 1, J = 7 Hz, C=CH); UV (95% EtOH) 239 nm (ε 9400), 296 (3000); mass spectrum (70 eV), m/e (relative intensity) 256 (M^+, 3), 228 (5), 226 (15), 191 (100), 69 (82). Anal. ($C_{12}H_{13}ClO_4$) C, H.

2-Propyl-4,4,5-trimethoxycyclohexa-2,5-dienone (7): mp 57–58 °C (ether–pentane); IR ($CHCl_3$) 1675, 1645, 1625 cm^{-1}; NMR (CCl_4) δ 0.95 (br t, 3, J = 7 Hz, CH_3C), 1.49 (m, 2, $-CH_2-$), 2.23 (br d, 2, J = 7 Hz, CH_2C=), 3.24 (s, 6, geminal OCH_3), 3.73 (s, 3, =C—OCH_3), 5.38 (s, 1, CO—CH=), 6.11 (br s, 1, C=CH); UV (95% EtOH) 235 nm (ε 12 300), 293 (3400); mass spectrum (70 eV), m/e (relative intensity) 226 (M^+, 6), 211 (32), 195 (73), 69 (100). Anal. ($C_{12}H_{18}O_4$) C, H.

2-Allyl-3,4,4-trimethoxycyclohexa-2,5-dienone (9): oil; IR (CCl_4) 1675, 1640, 1610 cm^{-1}; NMR (CCl_4) δ 3.03 (br d, 2, J = 6 Hz, C=CCH_2), 3.35 (s, 6, geminal OCH_3), 4.15 (s, 3, =C—OCH_3), 4.75–5.22 (m, 2, CH_2=C), 5.45–6.05 (m, 1, CH=C), 6.25 (d, 1, J = 10 Hz, CO—CH=), 6.47 (d, 1, J = 10 Hz, C=CH); UV (95% EtOH) 227 nm (ε 9100), 315 (3900); mass spectrum (70 eV), m/e (relative intensity) 224 (M^+, 11), 193 (57), 53 (100). Exact mass calcd for $C_{12}H_{16}O_4$: 224.10486. Found: 224.10649.

2-Allyl-4-methoxy-3,4-methylenedioxycyclohexa-2,5-dienone (11): oil; IR (CCl_4) 1700, 1660, 1615 cm^{-1}; NMR (CCl_4) δ 2.95 (br d, 2, J = 6 Hz, C=CCH_2), 3.25 (s, 3, $-OCH_3$), 4.73–5.17 (m, 2, CH_2=C), 5.53 (s, 1, $-OCH_2O-$), 5.58 (s, 1, $-OCH_2-$), 5.63–6.10 (m, 1, CH=C), 6.15 (d, 1, J = 10 Hz, CO—CH=), 6.70 (d, 1, J = 10 Hz, C=CH); UV (95% EtOH) 225 nm (ε 7200), 305 (3800); mass spectrum (70 eV), m/e (relative intensity) 208 (M^+, 6), 178 (100), 177 (59), 163 (52), 135 (66). Exact mass calcd for $C_{11}H_{12}O_4$: 208.07356. Found: 208.07298.

2,4-Dimethoxy-3,4-methylenedioxycyclohexa-2,5-dienone (13): mp 71–72 °C; IR (CCl_4) 1700, 1670, 1620 cm^{-1}; NMR (CCl_4) δ 3.28 (s, 3, C–OCH_3), 3.78 (s, 3, =C—OCH_3), 5.58 (s, 2, $-OCH_2O-$), 6.05 (d, 1, J = 10 Hz, CO—CH=), 6.78 (d, 1, J = 10 Hz, C=CH); UV (95% EtOH) 230 sh nm (ε 6200), 321 (3200); mass spectrum (70 eV), m/e (relative intensity) 198 (M^+, 5), 168 (100), 167 (72), 153 (57), 69 (94). Exact mass calcd for $C_9H_{10}O_5$: 198.05282. Found: 198.05355.

2,4,4,5-Tetramethoxycyclohexa-2,5-dienone (15): mp 158–159 °C (ethyl acetate); IR ($CHCl_3$) 1660, 1640, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.40 (s, 6, geminal OCH_3), 3.83 (s, 3, =C—OCH_3), 3.92 (s, 3, =C—OCH_3), 5.57 (s, 1, CO—CH=), 5.80 (s, 1, C=CH); UV (95% EtOH) 249 nm (ε 16 400), 304 (1800); mass spectrum (70 eV), m/e (relative intensity) 214 (M^+, 8), 199 (28), 183 (100), 171 (15), 155 (57), 140 (32), 125 (37), 69 (85). Anal. ($C_{10}H_{14}O_5$) C, H.

2,4-Dimethoxy-4,5-methylenedioxycyclohexa-2,5-dienone (17): mp 113–114 °C (chloroform–hexane); IR ($CHCl_3$) 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.44 (s, 3, C–OCH_3), 3.82 (s, 3, =C—OCH_3), 5.71, 5.74, 5.77, and 5.82 (four sets of s, 4, vinyl protons and $-OCH_2O-$); UV (95% EtOH) 252 nm (ε 17 600), 306 (1600); mass spectrum (70 eV), m/e (relative intensity) 198 (M^+, 4), 167 (50), 125 (41), 109 (54), 69 (100). Anal. ($C_9H_{10}O_5$) C, H.

2-(2,3-Dibromo-3-methylbutyl)-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (19): mp 112–113 °C (ether–hexane); one diastereoisomer; IR (CCl_4) 1690, 1660, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.96 (s, 3, CH_3), 2.08 (s, 3, CH_3), 2.66 (d of d, 1, J = 15 and 10 Hz, CH_AH_BC=), 3.46 (s, 3, $-OCH_3$), 3.65 (d of t, 1, J = 15, 2, and 2 Hz, CH_AH_BC=), 4.54 (d of d, 1, J = 10 and 2 Hz, CHBr), 6.63, 6.67 and 6.72 (three sets of s, 3, vinyl proton and $-OCH_2O-$), 6.91 (m, 1, vinyl proton); UV (95% EtOH) 238 nm (ε 9200), 297 (3800); mass spectrum (70 eV), m/e (relative intensity) 396 (M^+, absent), 287 (33), 285 (34), 259 (4), 257 (4), 205 (14), 151 (26), 69 (79), 53 (100). Anal. ($C_{13}H_{16}Br_2O_6$) C, H.

3,4,4-Trimethoxycyclohexa-2,5-dienone (21): mp 61 °C (ether–hexane); IR ($CHCl_3$)·1670, 1635, 1610 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 6, geminal OCH_3), 3.81 (s, 3, =C—OCH_3), 5.66 (d, 1, J = 2 Hz, CH=C—O), 6.32 (d of d, 1, J = 10 and 2 Hz, CO—CH=), 6.59 (d, 1, J = 10 Hz, C=CHC$(OCH_3)_2$); UV (95% EtOH) 224 nm (ε 10 700), 290 (4700); mass spectrum (70 eV), m/e (relative intensity) 184 (M^+, 5), 169 (69), 153 (100), 125 (74), 110 (51), 95 (46), 69 (82). Anal. ($C_9H_{12}O_4$) C, H.

Thallium(III) Nitrate Oxidation. 2,4-Dimethoxy-4,5-methylenedioxycyclohexa-2,5-dienone (17). A *vigorously* stirred solution of 2-methoxy-4,5-methylenedioxyphenol (**16**) (5.7 g) in methanol (350 mL) containing finely powdered potassium bicarbonate (13.0 g) at 0 °C was treated with thallium trinitrate trihydrate (13.5 g) in approximately 2-g aliquots over 5 min. The mixture was stirred for 1 min at 0 °C and treated with sodium bicarbonate solution (300 mL, saturated) and then with ether (300 mL). The mixture was extracted with ether (4 × 200 mL), and the combined organic layers were washed with sodium chloride solution (3 × 100 mL, saturated). The combined aqueous layers were further extracted with ether (2 × 50 mL); the total organic extracts were dried (K_2CO_3) and evaporated in vacuo. Crystallization of the resulting solid from chloroform–hexane gave the pure dienone **17**, 4.7 g (70%).

Ferric Chloride Oxidation. 2-Propyl-4,4,5-trimethoxycyclohexa-2,5-dienone (7). To a *vigorously* stirred solution of 3,4-dimethoxy-6-propylphenol (6) (2.28 g, 11.6 mmol) in methanol (70 mL) containing finely ground potassium carbonate (8.15 g, 58 mmol) was added ferric chloride (15.7 g, 58 mmol) in one portion. The resulting mixture was kept at room temperature with continuous stirring for 30 min, and it was then poured into a saturated sodium bicarbonate solution. The aqueous solution was extracted thoroughly with ether; the combined organic extracts were washed once with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 2.3 g (88%) of a pale yellow solid which appeared to be pure dienone 7 on the basis of spectroscopic evidence. Recrystallization from ether–pentane gave analytically pure dienone as white rods.

DDQ Oxidation. 2-Allyl-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (4). To a stirred solution of 2-allyl-4,5-methylenedioxyphenol (3) (1.78 g, 10 mmol) in methanol (100 mL) was added 2.5 g (11 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone followed by 100 mg of *p*-nitrophenol. The mixture was stirred at room temperature for 1 h, and the solvent was removed in vacuo. After the residue was taken up in ether, it was washed twice with saturated sodium bicarbonate and once with brine and dried ($MgSO_4$). The ether was then evaporated in vacuo to give an oil which was quickly filtered through a short column of silica gel with 40% ethyl acetate in hexane as solvent. Pure dienone 4 was obtained (1.84 g, 88%) as an oily solid which on recrystallization from ether–pentane gave white rods.

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686) and to the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

Registry No.—1, 533-31-3; 2, 57197-23-6; 3, 19202-23-4; 4, 64949-70-8; 5, 67271-92-5; 6, 6906-69-0; 7, 67271-93-6; 8, 66967-26-8; 9, 66967-27-9; 10, 67271-94-7; 11, 67271-95-8; 12, 23504-78-1; 13, 67271-96-9; 14, 20491-91-2; 15, 67271-97-0; 16, 21505-18-0; 17, 67271-98-1; 18, 67271-99-2; 19, 67272-00-8; 20, 2033-89-8; 21, 64701-03-7.

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Palladium-Catalyzed Reductions of α,β-Unsaturated Carbonyl Compounds, Conjugated Dienes, and Acetylenes with Trialkylammonium Formates

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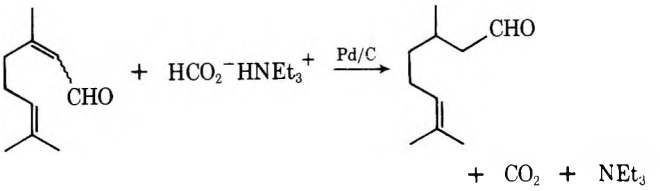
Received May, 5, 1978

We have reported the convenient reduction of halo- and nitroaromatic compounds with triethylammonium formate and a palladium catalyst.[1] The reaction is quite selective and provides two advantages over catalytic hydrogenation: it can be done in an open flask and it is very simple to measure the exact amount of reducing agent (formic acid) required. We have now found that the trialkylammonium formate–palladium system also is very effective and convenient for reducing α,β-unsaturated carbonyl compounds to saturated carbonyl compounds, and in some instances conjugated dienes and acetylenes to monoenes.

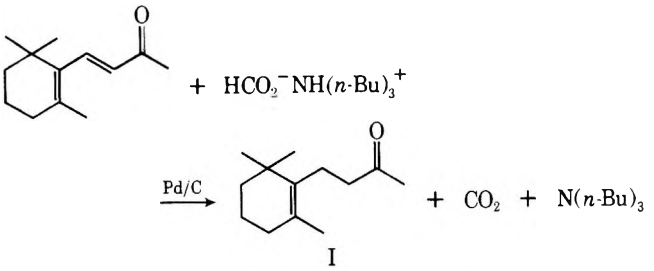
Results and Discussion

α,β-Unsaturated Carbonyl Compounds. A variety of α,β-unsaturated aldehydes, ketones, and esters were reduced at 100 °C with 10% excess formic acid, 30% excess triethyl- or tri-*n*-butylamine, and 1 mol % of palladium in the form of 10% palladium on carbon. The progress of the reductions could easily be monitored by measuring the amount of CO_2 evolved. We did this with several examples by carrying out the reactions in capped, thick-walled Pyrex bottles with a pressure gauge attached to a syringe needle inserted through the rubber liner of the bottle cap. Completion of the reaction was confirmed by GLC analysis. Products were isolated by filtering the solution from the catalyst and distilling the filtrate, or by first washing with aqueous acid and then distilling. The trialkylammonium formates generally form a second liquid phase in the reduction reaction, but dissociate and distill when heated. The compounds reduced by these procedures are listed in Table I.

Citral reduced rather slowly under our usual conditions (44 h) but very cleanly to citronellal in 91% (isolated) yield. Crotonaldehyde reduced more rapidly (8 h). Mesityl oxide, 2-

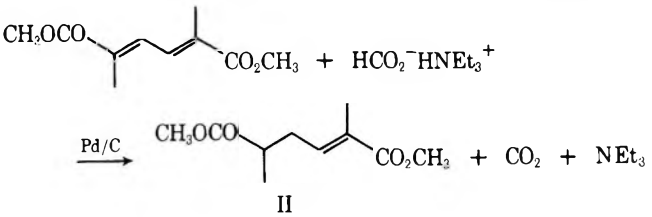


cyclopentenone, 3-methyl-2-cyclopentenone, and benzalacetone all reduced in high yields to the expected saturated ketones. The conjugated dienone, β-ionone, with 1.1 equiv of formic acid produced mainly (69%) the α,β-saturated enone, I. Only 2% of the α,β-unsaturated enone was formed. The remaining product was polymer.



I

Methyl crotonate, methyl cinnamate, and diethyl fumarate reduced to the saturated esters in high yield. Dimethyl (*E,E*)-2,5-dimethyl-2,4-hexadienedioate gave 96% of the monoene, II, under the usual conditions with only 4% completely saturated ester formed. Methyl sorbate gave a mixture of monoenes with methyl 2-hexenoate predominating (65%).



II

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Table I. Reductions with Trialkylammonium Formates[a]

compd	registry no.	amine[b]	time, h	product, % yield	registry no.
citral	5392-40-5	TE	44	citronellal, 91[c]	106-23-0
crotonaldehyde	4170-30-3	TE	8	butanal, 81[c]	123-72-8
mesityl oxide	141-79-7	TE	3	4-methyl-2-pentanone, 84[c]	108-10-1
2-cyclopentenone	930-30-3	TE	1.3	cyclopentanone, 83[c]	120-92-3
3-methyl-2-cyclopentenone	2758-18-1	TE	2.5	3-methylcyclopentanone, 87[c]	1757-42-2
benzalacetone	122-57-6	TB	2.5	4-phenyl-2-butanone, 86[c]	2550-26-7
β-ionone	14901-07-6	TB	20	I, 69[c,e]	17283-81-7
methyl crotonate	18707-60-3	TB	3.3	methyl butanoate, 83[c]	623-42-7
methyl cinnamate	103-26-4	TE	20	methyl hydrocinnamate, 86[c]	103-25-3
diethyl fumarate	623-91-6	TE	2.3	diethyl succinate, 81[c]	123-25-1
dimethyl (*E,E*)-2,5-dimethyl-2,4-hexadienedioate	23119-30-4	TE	2	II, 96[d,f]	67237-56-3
methyl sorbate	1515-80-6	TE	2	methyl 2-hexenoate, 65[d,g]	
methyl sorbate		TB	2	methyl 2-hexenoate, 62[d,g]	
methyl sorbate[h]		TE	2	methyl 2-hexenoate, 38[d]	
methyl sorbate[i]		TE	2	methyl 2-hexenoate, 37[d]	
crotononitrile	4786-20-3	TE	48	butanonitrile, 60[j]	109-74-0
1,3-cyclohexadiene	592-57-4	TE	21	cyclohexene, 72[d]	110-83-8
				cyclohexane, 8[d]	110-82-7
1,3-octadiene	1002-33-1	TE	3	1-octene, 28[c]	111-66-0
				2-octene, 51[c]	111-67-1
diphenylacetylene	501-65-5	TE	2	*cis*-stilbene, 93[c]	645-49-8
				dibenzyl, 2[c]	103-29-7
3-hexyne	928-49-4	TE[k]	1.3	*cis*-3-hexene, 70[c]	7642-09-3
				hexane, 18[c]	110-54-3
3-hexyne[h,m]		TE	30	*cis*-3-hexene, 85[d]	
				hexane, 6[d]	
1-hexyne	693-02-7	43TE[k]	3	1-hexene, 49[c]	
1-octyn-3-ol	818-72-4	TE	4	3-octanol, 56[c,l]	589-98-0
1-hexene	592-41-6	TE	7	hexane, 81[c]	

[a] Generally 20 mmol of substrate was reduced with 22 mmol of 95% formic acid and 0.2 mmol of palladium in the form of 10% palladium on carbon. The mixtures were heated at 100 °C in closed bottles for triethylamine reactions and in open flasks when tri-*n*-butylamine was used. [b] TE = triethylamine; TB = tri-*n*-butylamine. [c] Yield of isolated product or mixture of products. [d] Yield determined by GLC. [e] Also present in the product was 2% of the α,β-unsaturated ketone. [f] About 4% of dimethyl 2,5-dimethylhexanedioate was present. [g] About 35% of an isomeric methyl hexenoate was also formed. [h] The catalyst was 1% $Pd(OAc)_2$ and 2% tri-*o*-tolylphosphine. [i] The catalyst was 1% $Pd(OAc)_2$ and 2% tri(2,5-diisopropylphenyl)phosphine. [j] Only 60% of the crotonitrile had reacted in this time and the reaction appeared to have stopped. [k] Reaction mixture was heated at 75 °C for the time indicated. [l] Yield based upon formic acid. [m] Reacted at room temperature with the equivalent amount of formic acid.

We tried soluble palladium catalysts for this reduction attempting to improve the selectivity. Both diacetatobis(tri-o-tolylphosphine)- and diacetatobis(tri[2,5-diisopropylphenyl]phosphine)palladium(II) were less selective than 10% Pd/C as catalysts for this reduction.

Crotonitrile reduced very slowly and incompletely under the usual conditions to butanonitrile.

Conjugated Dienes. Simple conjugated dienes were reduced by the trialkylammonium formate catalysts mainly to monoenes. With a 10% excess of formic acid, 1,3-cyclohexadiene gave 72% cyclohexene and 8% cyclohexane. Similarly, 1,3-octadiene gave 28% 1-octene and 51% 2-octene.

Acetylenes. Diphenylacetylene reduced in 2 h at 100 °C to give 93% *cis*-stilbene and 2% dibenzyl. Other acetylenes did not reduce as cleanly, however. 3-Hexyne, even with exactly 1 equiv of formic acid, gave 70% *cis*-3-hexene and 18% hexane. With the soluble bis(tri-o-tolylphosphine)palladium acetate catalyst reduction at room temperature was slow but *cis*-3-hexene was formed in 85% yield with only 6% hexane produced. 1-Hexyne under the usual conditions gave pure 1-hexene but only in 49% yield. The remainder of the product was polymer. 1-Octyn-3-ol also reduced poorly giving only 3-octanol in 56% yield and polymer. No olefin was formed. We carried out a reduction of 1-hexene to compare its reactivity with that of the 1-hexyne. It reduced less than half as rapidly in good yield to hexane (81%).

Summary. The trialkylammonium formate–palladium on carbon catalyst system is a very convenient combination for reducing α,β-unsaturated aldehydes, ketones, and esters to the saturated carbonyl compounds in high yields under mild conditions. Conjugated dienes reduce to monoenes with 1 equiv of reagent fairly selectively while terminal acetylenes give considerable polymer as well as olefin except for 1-octyn-3-ol which gives only 3-octanol. 3-Hexyne and diphenylacetylene give good yields of *cis*-olefins.

Experimental Section

Materials. The 10% palladium on carbon was obtained from the Research Organic/Inorganic Chemical Corp. The palladium acetate and arylphosphines were the materials described previously.[2] The tertiary amines were commercial samples (Aldrich) that were dried over 4 Å molecular sieves before use. Methyl sorbate was prepared by the sulfuric acid catalyzed esterification of sorbic acid (Aldrich) and the (*E,E*)-dimethyl 2,5-dimethyl-2,4-hexadienedioate was prepared by the literature method.[3] All other materials were commercial samples which were used without further purification.

General Procedure for Reductions. Capped Bottle Reactions. Heavy-walled Pyrex bottles of 250-mL capacity were used. In the bottle were placed a magnetic stirring bar, 0.21 g 10% Pd on carbon (0.20 mmol Pd), 20 mmol of the compound to be reduced, and 4 mL (29 mmol) of triethylamine. The bottle was then capped with a self-sealing rubber-lined cap and 0.83 mL (22 mmol) of 95% formic acid was added by microsyringe through the rubber cap liner. A pressure gauge attached to a syringe needle was injected through the cap and the bottle was stirred at 100 °C in a steam bath until the pressure stopped increasing. Completion of the reaction was then confirmed by GLC analysis. Products were isolated by filtration of the catalyst and distillation of the filtrate or concentration of the filtrate and recrystallization.

Reactions in Open Flasks. The same molar quantities of reactants as above were placed in a 50-mL three-necked round-bottomed flask. The mixture was stirred on the steam bath until GLC analysis of a small sample of the reaction mixture showed complete reaction had

occurred. Products were isolated by filtration, rinsing with methylene chloride and washing the filtrate with 10% hydrochloric acid to remove the amine. After drying with anhydrous magnesium sulfate the solution was concentrated and the residue was either distilled or recrystallized.

The properties of products prepared and the means of identification employed are listed in Table II which will appear only in the microfilm edition of this journal.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of the research.

Registry No.—*trans*-methyl 2-hexenoate, 13894-63-8; *cis*-methyl 2-hexenoate, 13894-64-9; Pd, 7440-05-3; TE formate, 585-29-5; TB formate, 7204-61-7.

Supplementary Material Available: Table II, listing the properties of the products prepared (2 pages). Ordering information is given on any current masthead page.

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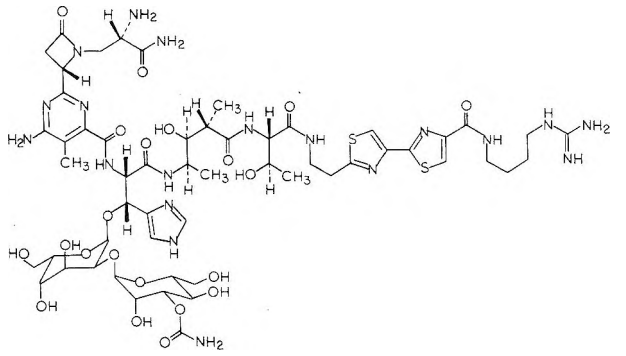
Communications

Synthesis of L-Gulose from D-Glucose via Aldose Interchange

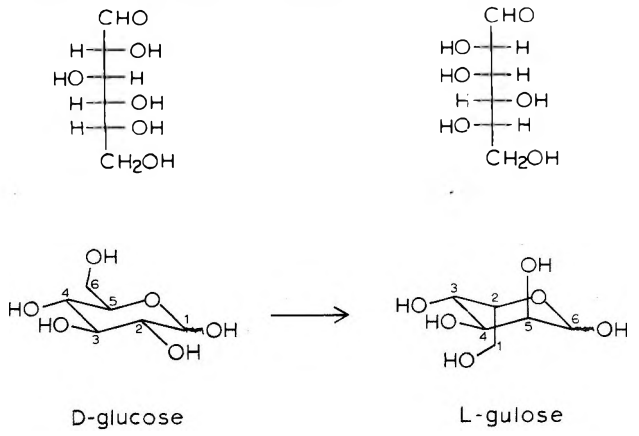
Summary: L-Gulose has been prepared from D-glucose in a form suitable for reconstruction of bleomycin.

Sir: Bleomycin (**1**) is an antitumor antibiotic possessing clinically useful activity in the treatment of squamous cell carcinomas.[1] Our interest in the total synthesis of bleomycin B_2 (**1**) has prompted us to consider practical methods for



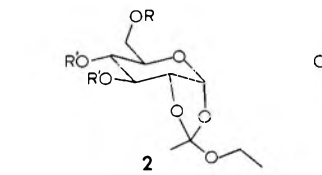
1

preparation of the rare sugar L-gulose in a form suitable for synthetic elaboration of the carbohydrate moiety of bleomycin. Since gulose must be attached stereoselectively to L-*erythro*-β-hydroxyhistidine and 3-*O*-carbamoylmannose via O-1 and O-2, respectively, the sugar must be prepared in a form that permits O-1 and O-2 to be differentiated from each other, and from O-3, O-4, and O-6, in subsequent synthetic transformations. Therefore, while syntheses of L-gulose have been reported,[2] none of these was suitable for our purposes; we report herein an efficient synthesis of an appropriate L-gulose derivative.



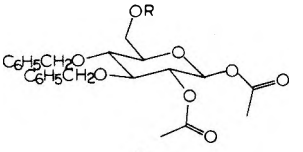
D-glucose L-gulose

Fischer recognized the conceptually simple relationship between the readily available D-glucose and L-gulose, which differ only in oxidation state at C-1 and C-6, and utilized this principle for the preparation of L-gulose from D-glucaric acid in low yield by successive reductions with sodium amalgam.[2a] In the present case, more direct interconversion has been achieved by oxidation of 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-D-glucopyranose (**3b**) to the corresponding 6-aldehydo sugar [isolated as the respective *N,N*-dimethylhydrazone (**4**)] and subsequent borohydride reduction of the latent dialdehyde with sodium borohydride, affording the desired 3,4-di-*O*-benzyl-1-(*N,N*-dimethylhydrazino)-L-gulopyranose (**5**) as a clear oil in 42% overall yield from D-glucose. Verification of structure was accomplished by conversion to 1,6-anhydro



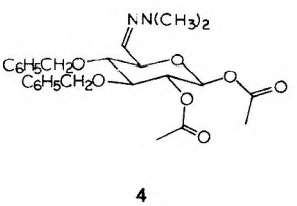
2

a R,R′ = $COCH_3$
b R = $C(C_6H_5)_3$, R′ = H
c R = $C(C_6H_5)_3$, R′ = $CH_2C_6H_5$



3

a R = $C(C_6H_5)_3$
b R = H



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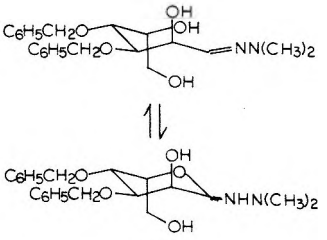

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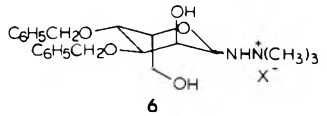

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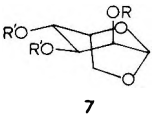

7

a R = H, R′ = $CH_2C_6H_5$
b R, R′ = $COCH_3$
c R, R′ = H

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sugars **7b** and **7c**, the optical antipodes of which are known species.[3]

Glucopyranosyl diacetate **3b**, obtained in 80% overall yield from **2a** (→ **2b** → **2c** → **3a** → **3b**),[4] was chosen as the substrate for terminal functionality interchange to provide a suitably blocked L-gulose derivative. Initial efforts to effect oxidation at C-6 (e.g., with $SO_3 \cdot C_6H_5N$, Me_2SO,[5] or pyridinium chlorochromate[6]) gave unstable products reactive with dinitrophenylhydrazine, in addition to benzaldehyde.[7] Analysis by NMR suggested major structural alterations, including possible epimerization at C-5 as well as loss of the well-defined signals corresponding to the anomeric and acetate methyl protons.[8] To obviate the loss of the acetate moieties, which would render chemically indistingishable the aldehyde groups at C-6 and C-1, a less acidic oxidant was employed. Thus **3b** was treated with *N*-chlorosuccinimide–dimethyl sulfide[9] (4 h, −25 °C) to give a chromatographically homogeneous, albeit unstable product [IR 1710 cm^{-1}; NMR δ 1.93 (s, 3), 2.05 (s, 3), and 9.59 (s, 1)] which was immediately converted to the respective *N,N*-dimethylhydrazone (**4**)[10] [1 equiv of $(CH_3)_2NNH_2$, 2 equiv of $(C_2H_5)_3N$, 25 °C, 18h], isolated as colorless needles in 66% yield (based on **3b**): mp 146–147 °C; $[\alpha]^{25}_D$ +56° (c 3.3, $CHCl_3$); NMR [$CDCl_3$, $(CH_3)_4Si$] δ 1.94 (s, 3), 2.07 (s, 3), 2.85 (s, 6), 3.6–4.3 (envelope, 3), 4.75 (m, 4), 4.93–5.30 (m, 1), 5.72 (d, 1), 6.28 (d, 1), and 7.33 (s, 10).

Transformation of diacetate **4** to 2,2-dimethylhydrazinyl 3,4-di-*O*-benzyl-L-gulopyranoside (**5**) may be envisioned via removal of the acetates and reduction of the C-1 aldehyde. Although consideration of the intermediates involved in the conversion **4** → **5** suggests a number of possible competing processes,[11] treatment of **4** with catalytic $NaOCH_3$ (48 h, 25 °C) effected deacetylation without epimerization at C-5 or C-2.[12] The diol thus obtained was reduced with $NaBH_4$ (1 equiv, C_2H_5OH–H_2O) and the product was isolated as a chromatographically homogeneous white foam in quantitative yield (based on **4**) by extractive workup of the residue remaining after concentration of the reaction mixture; the product consisted of a 70:30 equilibrium mixture of hydrazino glycoside–acyclic hydrazone, as judged by NMR:[13] [$CDCl_3$, $(CH_3)_4Si$] δ 2.42 (s, 0.6), 2.49 (s, 3.6), 2.72 (s, 1.8), 3.1–4.1 (envelope, 7), 4.3–5.0 (envelope, 5), 6.73 (d, 0.3, J = 5 Hz), and 7.3 (s, 10).

Confirmation of the D-glucose → L-gulose transformation was obtained by conversion of species **5** (→ **6** → **7a** → **7b** → **7c**)[4] to crystalline 1,6-anhydro gulose derivatives **7b** and **7c**, the optical antipodes of which have been prepared and characterized.[3] The facile preparation of gulose derivatives **5** and **6**[14] provides intermediates of potential utility for elaboration of the carbohydrate moiety of bleomycin and establishes an efficient procedure for (formal) carbohydrate epimerizations by functionalization of nonchiral carbon atoms.

Acknowledgments. We thank Dr. Ki-Hyup Kim and Mr. Daniel Lieberman for assistance with optimization of certain synthetic transformations. This investigation was supported in part by contract NO1-CM 43712 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

Supplementary Material Available: Details of the conversion of **2a** to **3b** and **5** to **7b** and **7c** (3 pages). Ordering information is given on any current masthead page.

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(8) The latter changes probably occurred as a consequence of the Lewis acid catalyzed conversion of the 1,2-diacetate to an acetoxonium ion.
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(11) E.g., loss of stereochemistry at C-2 via the Lobry de Bruyn-Alberda van Ekenstein transformation (E. F. L. J. Anet in "The Carbohydrates. Chemistry and Biochemistry", Vol. IA, W. Pigman and D. Horton, Eds., Academic Press, New York, N.Y., 1972, pp 175 ff) and at C-5 in analogy with the putative intermediates in the Amadori rearrangement [J. E. Hodge, *Adv. Carbohyd. Chem.*, **10**, 169 (1955)], the latter of which could also result in transformation to an acyclic C-5 keto sugar.
(12) The integrity of these stereochemical centers may be inferred from the lack of significant alteration of the chemical shifts of the methylhydrazinyl (δ 2.78) and C-6 (δ 6.33) hydrogens and of the coupling constant (J = 5 Hz) of the latter, as well as the observed coupling constant (J = 3 Hz) between the equational anomeric hydrogen and the C-2 hydrogen [R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966)].
(13) Assigned by consideration of the chemical shifts of the hydrazino methyl signals and C-1 hydrogen: the singlet at δ 2.72 represented 30% of the integrated intensity corresponding to the methyl hydrogens; the doublet at δ 6.73 (J = 5 Hz) constituted one-sixth of this, suggesting that these signals were attributable to the acyclic hydrazone [G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3923 (1968)]. The remaining integrated intensity appeared as singlets at δ 2.49 and 2.42 (6:1) and was attributed to the hydrazinylglycoside (**5**).
(14) The facile displacement of trimethylhydrazine from **6** suggests the possible utility of this compound (or some suitable O-6-substituted derivative) in the preparation of the carbohydrate moiety of bleomycin.
(15) National Cancer Institute Postdoctoral Trainee, 1975–1977.
(16) National Cancer Institute Career Development Awardee, 1975–1980. Alfred P. Sloan Research Fellow, 1975–1979. John Simon Guggenheim Fellow, 1977–1978.

David K. Minster,[15] Sidney M. Hecht*[16]
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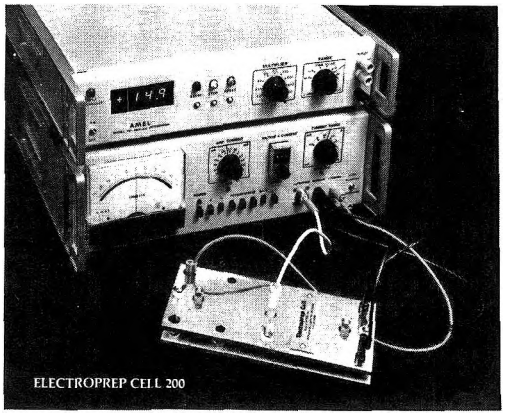

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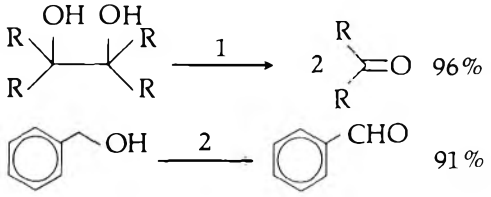

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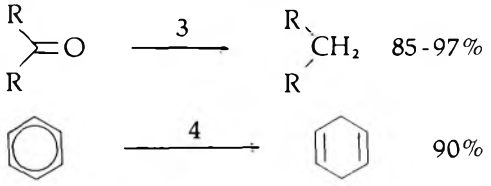

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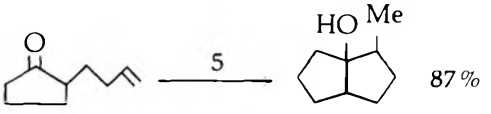

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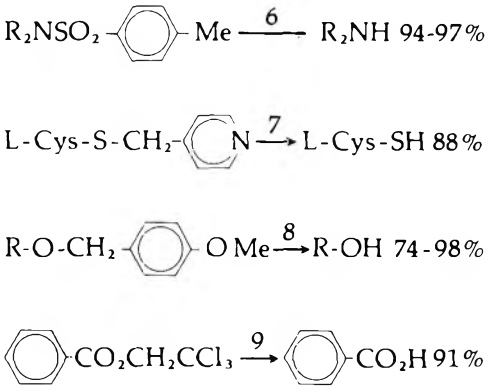
DEPROTECTIONS



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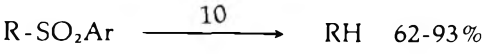

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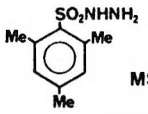
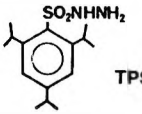
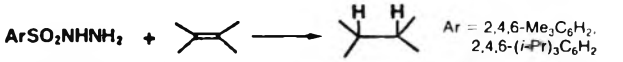


MSH



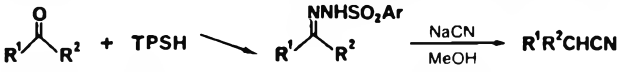
TPSH

2,4,6-Trimethylbenzenesulfonyl hydrazide (mesitylenesulfonyl hydrazide, MSH) and **2,4,6-triisopropylbenzenesulfonyl hydrazide (TPSH)** are effective and convenient sources of diimide for the reduction of olefins and azo compounds (**TPSH** is more reactive). Reaction conditions are



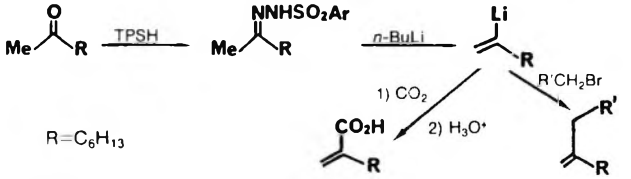
quite mild; typically, a two-fold excess of the sulfonyl hydrazide with the olefin in refluxing methanol, ether, or THF gives a 60-100% yield of reduced olefin. Azobenzene affords quantitative yields of hydrazobenzene under a variety of conditions.[1]

The hydrazones of **TPSH** and aldehydes and ketones react with sodium cyanide in methanol at reflux to afford moderate to good yields of nitriles.[2] The analogous hydrazones of *p*-toluenesulfonyl hydrazide require heating in



decalin at 180° and, even under these conditions, the competing elimination of hydrogen cyanide regenerates the hydrazone.[3]

Bond and coworkers[4] have shown that the hydrazones of **TPSH** and aldehydes or ketones afford vinyllithium compounds upon treatment with 2.2-3.0 equivalents of *n*-butyllithium at -78° in TMEDA-hexane.



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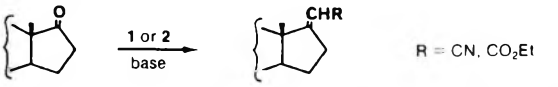
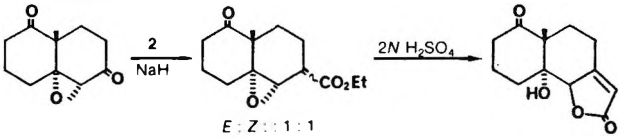
Wittig-Horner Reagents

The Wittig reaction of carbonyl compounds with phosphonium ylides to form olefins is widely used in academic and industrial laboratories.[1] Modification of such an olefin synthesis with organic phosphonate carbanions[2] is widely referred to as the Wittig-Horner reaction.

Carbonyl compounds, including the hindered 17-keto-steroids, react with **diethyl (cyanomethyl)phosphonate (1)** or **triethyl phosphonoacetate (2)** in the presence of a base to yield the corresponding α,β-unsaturated nitriles[3,4] or esters,[4] respectively.



The Wittig-Horner reaction of epoxy ketones with **2** and sodium hydride, followed by acid hydrolysis, yields α,β-unsaturated γ-lactones.[5]



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Gallagher and Webb[6] reported the novel use of **triethyl 2-phosphonopropionate (3)** with a variety of ketones to form tetrasubstituted acrylates in high yield.[7]

Aldrich is pleased to add **triethyl 2-phosphonopropionate (3)** to its list of Wittig reagents.

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