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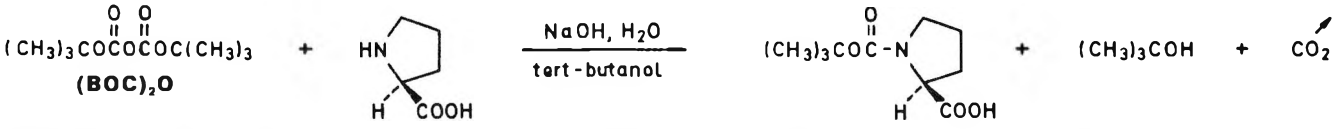

120 g (0.55 moles) di-tert-butyl dicarbonate were added dropwise within an hour to a well stirred solution of 57.6 g (0.5 moles) L-proline and 20.0 g (0.5 moles) sodium hydroxide in 50 ml water and 100 ml tert-butanol. After a short induction period, the temperature rose to 45° (without external cooling). The reaction was brought to completion after the addition of a further 100 ml tert-butanol, and stirring overnight. The turbid solution was diluted with 250 ml water and extracted with three times 300 ml pentane. The aqueous phase was acidified to pH 2-3 by the addition of 70 g potassium hydrogen sulfate in the cold and extracted with four 400 ml portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was removed at 35-40° under reduced pressure in a rotary evaporator and the residue finally dried at 0.5 mm to constant weight. Yield: 105.5 g (98%) colourless crystalline material; m.p. 131.6-132.7°; $[\alpha]_{546}^{20}$ −71.07° (c = 2 in acetic acid). Dieter Emmerich and Walter Keller c/o Fluka AG.

References for representative preparations of BOC-L-proline (with reported yields and reagents used)

G.W. Anderson, A.C. McGregor, "t-Butyloxycarbonylamino acids and their use in peptide synthesis", J. Am. Chem. Soc. *79* (1957), 6180 (Yield 55% with tert-butyl-4-nitrophenyl carbonate)

E. Schnabel, "Verbesserte Synthese von tert.-Butyloxycarbonyl-aminosäuren durch pH-Stat-Reaktion", Ann. Chem. *702* (1967), 188 (Yield 96% with tert-butyloxycarbonyl azide)

T. Nagasawa, K. Kuriowa, K. Narita, Y. Isowa, "New agents for t-butyloxycarbonylation and p-methoxybenzyloxycarbonylation of amino acids", Bull. Chem. Soc. Jap. *46* (1973), 1269 (Yield 96% with tert-butyl-4,6-dimethylpyrimidyl-2-thiol carbonate)

U. Ragnarsson, S. M. Carlsson, B. E. Sandberg, L. E. Larsson, "tert-Butyloxycarbonyl-L-proline", Org. Synth. *53* (1973), 25 (Yield 83-90% with tert-butylphenyl carbonate)

V. F. Pozdnev, "Use of di-tert-butyl pyrocarbonate to obtain N-tert-butoxycarbonyl derivatives of amino acids", Khim. Prir. Soed. (1974), 764 (Yield 95%)

N. Itoh, D. Hagiwara, T. Kamiya, "A new tert-butyloxycarbonylating reagent, 2-tert-butyloxycarbonyloxyimino-2-phenylacetonitrile", Tetrahedron Lett. (1975), 4393 (Yield 88%)

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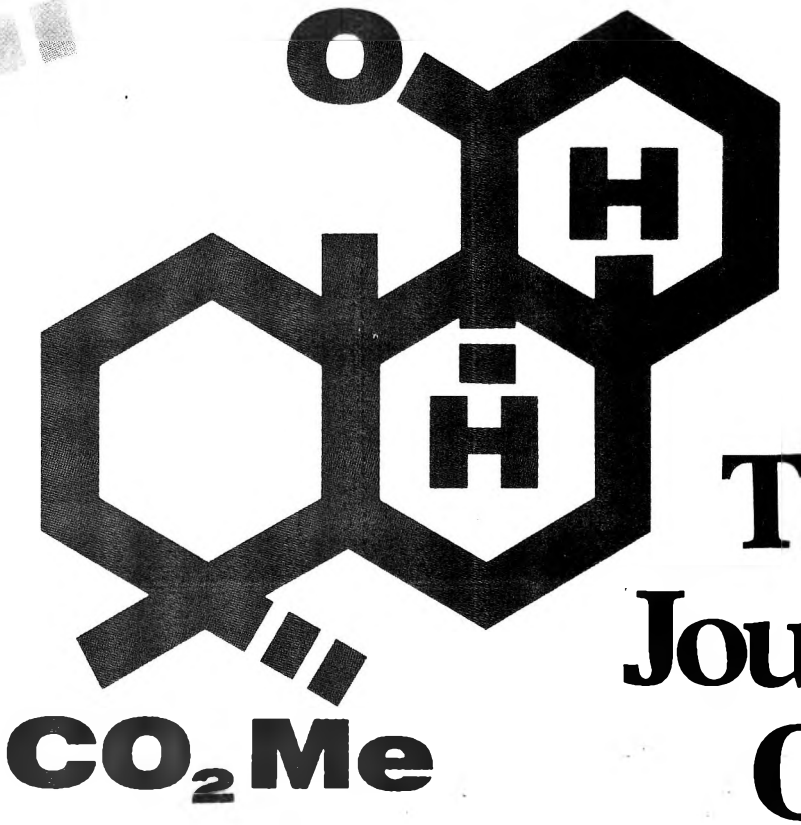

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Thiyl Radical Induced Cyclizations of Dienes. Cyclization of α-Acoradiene, α-Bulnesene, and Geranyl Acetate to Cedrane, Patchulane, and Cyclogeranyl Acetate Products

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Received August 10, 1976

Selected dienes reacted with ethanethiol, dimethyl disulfide, diphenyl disulfide, and bis(trifluoromethyl) disulfide, with radical initiation by photolysis of diphenyl disulfide or thermolysis of benzoyl peroxide, to give thiyl substituted cyclization products and acyclic adducts. These were desulfurized with Raney nickel. Thus diallylmalonate and diallylacetate gave good yields of *cis*- and *trans*-dimethylcyclopentanes (6:1 or total stereoselectivity), α-acoradiene was quantitatively coverted to cedrane, and α-bulnesene gave a modest yield of dihydro-α-patchulene in addition to tetrahydrobulnesene. Geranyl acetate led to various ratios of cyclic and acyclic adducts (5:1 to 1:17) depending on reaction conditions. No significant cyclization was found with aromatic olefins. The results suggest a stabilization of intermediate radicals with α-thiyl substituents not found with corresponding oxygen substituents.

While cyclizations of dienes and polyenes through carbonium ion intermediates have been extensively studied with respect to structural[2-5] and stereochemical[6-8] parameters and encompass major synthetic[9] and biomimetic[10,11] routes to carbocyclic systems, radical-initiated cyclizations of dienes have only been explored in recent years.[12-15] The two processes can differ fundamentally in synthetic direction, allowing alternative preferential ring size formation. In cationic cyclizations six-membered rings are generally obtained, with divergence to five-membered rings associated with examples of increased electronic stabilization of carbonium ion intermediates (increased alkyl substitution of cationic centers) when competing six-membered ring formation does not show this advantage.

In contrast, radical-initiated cyclizations generally lead to five-membered rings. Electronic stabilization of intermediate cyclized product radicals seems less important[14a] than considerations of steric compression in the cyclization process[16] or electronic stabilization of an initially reacting radical center,[14a] which may cause reversal of a kinetically favored five-membered ring closure. Thus six-membered rings can sometimes be obtained as a result of these two factors. Further control of cyclization arises from the required orbital overlap of the π system with the electron-deficient reacting center.[17] This results in the usual requirement of having at least three atoms between the double bond and the reacting center with consequent possibility of regiospecific direction of addition of an initiating agent in cyclizations of dienes.

The present study of thiyl radical induced cyclizations was undertaken because reductive desulfurization of cyclization products could allow alternatives to proton initiated cyclizations with respect to isomeric product type and/or compatibility with acid-sensitive functional groups, i.e., allylic oxygen or ketal functions. It was also of fundamental interest to see if the reversibility of thiyl radical addition to olefins[18] and the possibility of interaction of a radical center with a β-thiyl substituent[19,20] might furnish results which would reflect the energetic requirements of the radical cyclization process.

In order to get a comparison of cyclizations effected by representative thiyl radical species, dimethyl diallylmalonate (1) was subjected to reactions with ethanethiol without a radical initiating reagent and with radical initiation by photolysis with a small amount of diphenyl disulfide, or by initiation of the reaction with dibenzoyl peroxide. Thiyl radical addition and cyclization was also obtained by photolysis of

Scheme I. Reactions of Dimethyl Diallylmalonate with Thiyl Radicals Derived from Ethanethiol or Dialkyl Disulfides

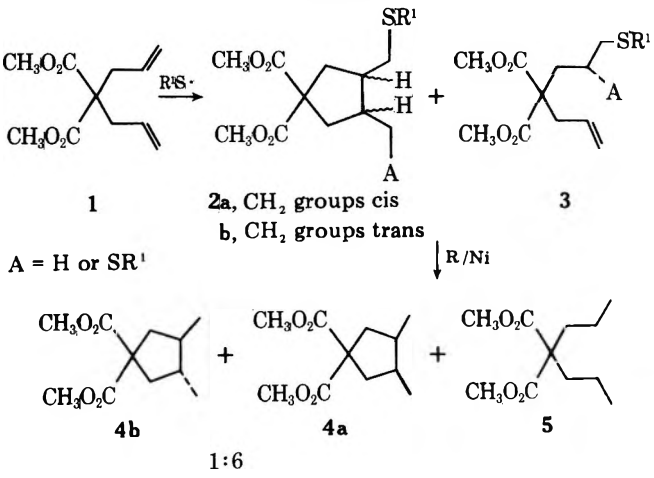


Table I. Reactions of Dimethyl Diallylmalonate with Thiyl Radicals

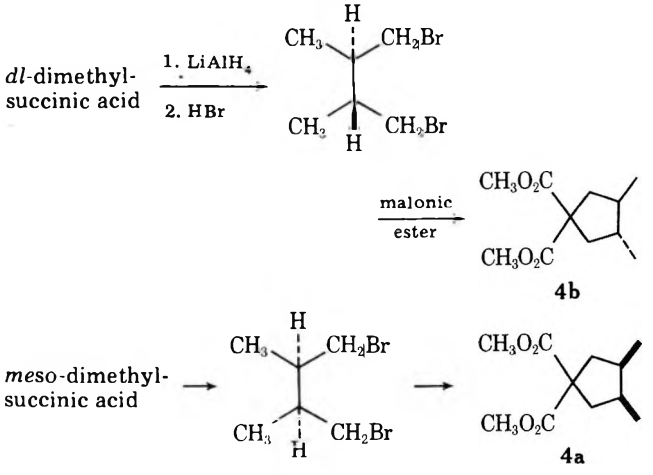
Reaction conditions	Yield, % Cyclic adducts 2 (a:b)	Acyclic adducts 3
Ethanethiol, diphenyl disulfide, $h\nu$, neat	85 (6:1)	6
Ethanethiol, diphenyl disulfide, $h\nu$, benzene	92 (6:1)	6
Ethanethiol, benzoyl peroxide, heat, neat	73 (4:1)	3
Ethanethiol, benzoyl peroxide, heat, benzene	<1[a]	
Ethanethiol, RT, dark 15 h, neat	25[b] (1:trace)	15
Dimethyl disulfide, $h\nu$, neat	83[c] (only 2a)	7
Bis(trifluoromethyl) disulfide, $h\nu$, neat	48[d]	14

[a] >90% recovery of starting material. [b] 60% recovery of starting material. [c] Mixture of methanethiol and some dimethyl disulfide adducts. [d] Estimated from desulfurization products of 11-component mixture.

dimethyl disulfide. Reductive desulfurization of the reaction products **2a,b** and **3** on Raney nickel gave 3,4-dimethyl-1,1-dicarbomethoxycyclopentanes (**4a,b**) as a stereoisomeric mixture with the cis dimethyl compound as the major (6:1) or only isomer as well as dimethyl dipropylmalonate (**5**) as a minor product. While an analogous reaction with bis(trifluoromethyl) disulfide gave a product mixture with at least 11 components, subsequent reduction of this mixture again led primarily to the dimethylpentane product **4a.** These results are summarized in Table I.

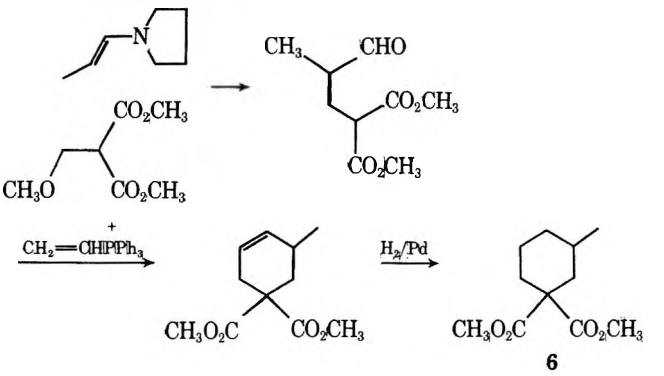
Adducts **2a,b** and **3** were characterized by mass fragmentography. Products **5** and **4a,b** were identified by VPC comparison with authentic samples, prepared respectively by hydrogenation of the diallyl compound **1** and the reaction sequence shown below,[21,22] which established the stereochemical assignment of epimers **4a,b.** Products **2a** and **4a** also

Scheme II. Syntheses of *cis*- and *trans*-3,4-Dimethylcyclopentanedicarboxylic Esters



gave NMR spectra consistent with dimethyl cyclopentanedicarboxylic esters. In order to rule out formation of a minor six-membered cyclization product, dicarbomethoxy-3-methylcyclohexane (**6**) was prepared from the enamine derivative of propionaldehyde, dimethyl methoxymethylmalonate, and triphenylvinylphosphonium bromide by the indicated reactions. The final product **6** of this reaction sequence was not found among the desulfurized thiyl radical cyclization products.

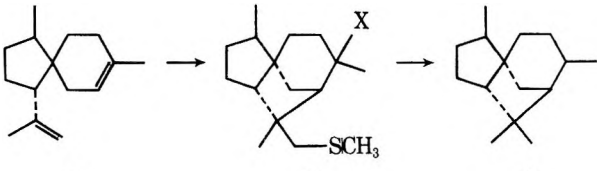
Scheme III. Synthesis of 1,1-Dicarbomethoxy-3-methylcyclohexane



The results conform with analogous, stereochemically unclassified, radical-initiated cyclizations of diallyl compounds.[21,23] The stereospecificity of the cyclization leading to the thermodynamically unfavored cis dialkylcyclopentane product **2a** may be contrasted with the predominant formation of trans substituted cyclopentane products from cyclization of benzylic 6-arylhex-1-enyl radicals,[24] and the previously assumed formation of trans substituted cyclopentanes as other diallyl cyclization products.[14b,g] Generation of cis-disubstituted cyclopentane products can be presumed to arise from a kinetic control based on stereoelectronic factors. The latter may be complex since the cis–trans ratio was found to vary for the same reactants with changes in experimental conditions and thus several alternative postulates may have to be considered.[25]

Irradiation of solutions of α-acoradiene (**7**)[26] and dimethyl disulfide in benzene or cyclohexane yielded nearly quantitatively 1:1 adducts **8** of the diene and methanethiol (96%, *m/e* 252) and dimethyl disulfide (4%, *m/e* 298). Raney nickel desulfurization of this product gave a saturated hydrocarbon **9** (*m/e* 206) which was identified as dihydrocedrene by com-

Scheme IV. Reaction of α-Acoradiene with Dimethyl Disulfide and Desulfurization



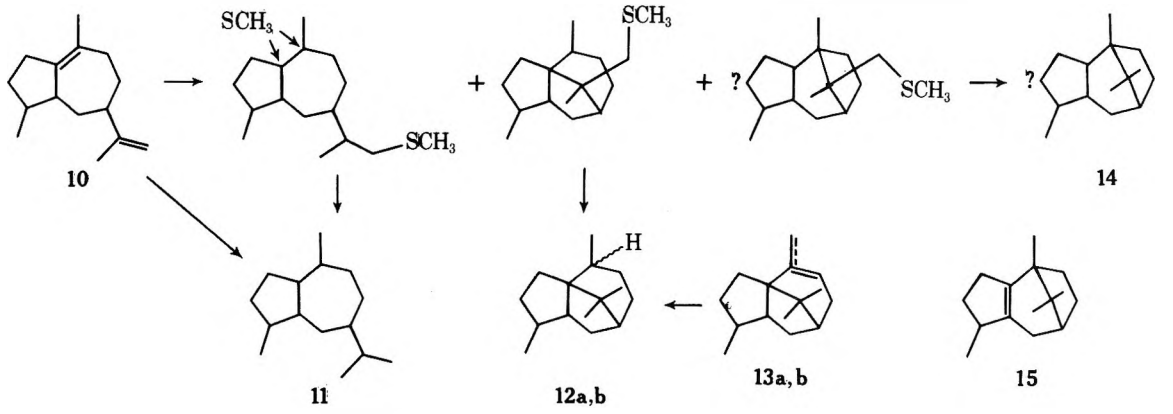
X = H and SCH_3

parison of IR and NMR spectra, the mass fragmentation pattern, and VPC retention times with those of the hydrogenation product of natural cedrene. Tetrahydroacoradiene was not found.

Photolysis of dimethyl disulfide and α-bulnesene[27] (**10**) in cyclohexane or benzene gave complex mixtures of products. Desulfurization of these yielded tetrahydrobulnesene (**11**) as a major component and at least five other compounds. One of these was identified as a dihydro-α-patchulene **12a,b** by comparison of its mass fragmentation with that of one of the two epimeric products obtained on hydrogenation of a mixture of α- and γ-patchulenes **13a,b.** A further isolated isomeric saturated product could not be definitely assigned the alternative dihydro-β-patchulene structure **14** because of failure to obtain a stereoisomerically corresponding pure product from β-patchulene (**15**).

The extensive formation of uncyclized adducts of bulnesene contrasts with the preceding examples of five-membered ring formation in high yields. It may be ascribed to strain in the bridged ring systems[28] **12** and **14** and to steric compression

Scheme V. Reactions of Bulnesene with Dimethyl Disulfide and Desulfurization

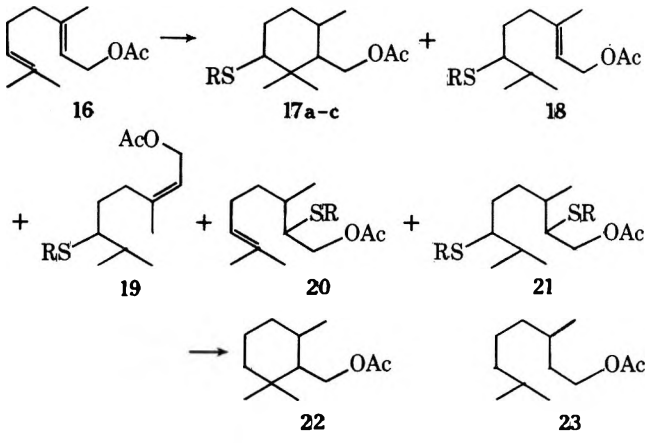


arising from four geminal substituents on the generated five-membered ring. Avoidance of such 1,2-tetrasubstituted cyclopentane products was again found in the following radical cyclizations.

In reactions of geranyl acetate (16) with thiyl radicals, attack at the less substituted position of the terminal double bond produces a tertiary radical which could undergo cyclization to five- or six-membered rings. If steric compression by four adjacent geminal substituents is a barrier to the former course, the alternative (otherwise slower) cyclization to a six-membered ring and competing hydrogen abstraction by the radical, with formation of acyclic thiol adducts, can be anticipated as preferred reaction pathways. Acyclic addition products rather than cyclization should also result from thiyl radical addition to the internal double bond since the tertiary radical thus formed would have poor overlap with the terminal double bond (only two carbons between the double bond and radical center). Table II shows the ratio of acyclic to cyclic compounds obtained after desulfurization of reaction products formed in various thiyl radical reactions with geranyl acetate.

Generally six monothioether fractions were obtained from reactions of ethanethiol or dimethyl disulfide, consisting of three epimeric cyclization products **17a–c** and three acyclic fractions containing the adducts **18–20** (with the last possibly

Scheme VI. Reactions of Geranyl Acetate with Thiyl Radicals



as an epimeric mixture). A seventh fraction corresponding to epimeric diadducts **21** was formed in substantial amount in photolyses of dimethyl disulfide and geranyl acetate in cyclohexane or benzene. The product fractions were separated by VPC and characterized by NMR spectra and mass fragmentography.

Desulfurization of the thioethers with Raney nickel yielded cyclogeranyl acetate (**22**) and tetrahydrogeranyl acetate (**23**),

Table II. Ratios of Cyclic to Acyclic Product in the Reaction of Geranyl Acetate with Thiyl Radicals

RS source	Conditions	Acyclic	Cyclic	% reaction
EtSH	$h\nu$,[f] Pyrex,[g] PhSSPh, 15 h	9.4	1[a]	31
	$h\nu$, Pyrex, 68 h, PhH, PhSSPh	(95% starting material)		
	$(PhCO_2)_2$, 85 °C, 15 h	(92% starting material)		
	$(PhCO_2)_2$, 85 °C, 15 h, PhH	(99% starting material)		
$(CH_3S)_2$	$h\nu$, Pyrex, 17 h	4.75	1[a]	50
	$h\nu$, Pyrex, cyclohexane, 24 h	2.45	1[d]	45
		1	1.8[b]	
		1	0[c]	
	$h\nu$, Pyrex, benzene, 24 h	1.95	1[d]	33
PhSSPh	$h\nu$, Vycor, CH_3CN, 24 h	1	1.84[a]	18[e]
	$h\nu$, Pyrex, benzene, 24 h	1	5.1[a]	20[e]
	$h\nu$, Pyrex, cyclohexane, 24 h	1.25	1[a]	68
$(CF_3S)_2$	2537 Å, 15 h	16.6	1[d]	46[e]
	$h\nu$, Pyrex, 8 h	16.6	1[d]	56[e]
	$h\nu$, Pyrex, cyclohexane, 24 h	2.75	1[d]	56[e]
t-Bu_2S_2	$h\nu$, Vycor,[g] CH_3CN, 24 h	3.21	1[a]	17

[a] Based on desulfurization of starting-material-free product fraction. [b] Based on desulfurization of fraction corresponding to diene + CH_3SH. [c] Based on desulfurization of fraction corresponding to diene + $2CH_3SH$. [d] Based on desulfurization of total reaction mixture. [e] Recovery of volatile materials. [f] All photolyses with a 450-W Hg high-pressure lamp. [g] Light filter.

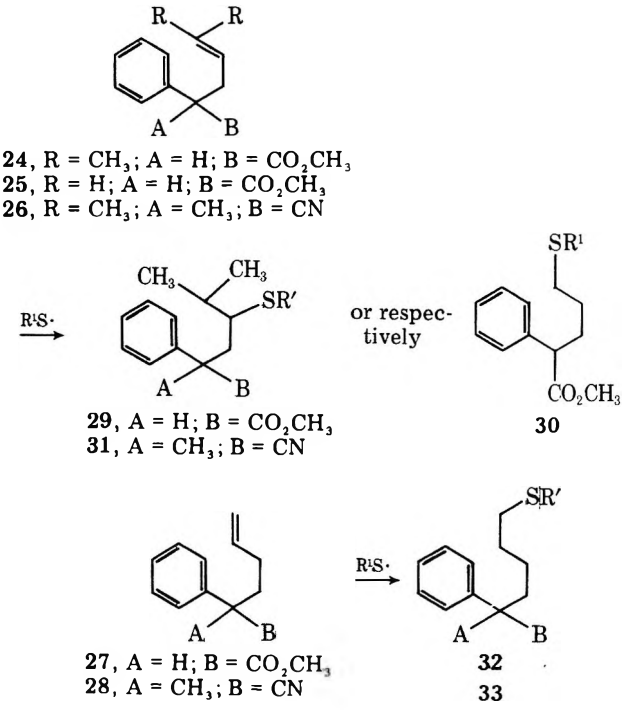
identified by comparison with authentic samples. In all of these thiyl radical reactions additional nonvolatile material was formed. Raney nickel desulfurization of these distillation residues did not produce volatile products.

Photolysis of diphenyl disulfide and geranyl acetate in benzene gave a higher cyclization ratio (5:1) than ethanethiol or dimethyl disulfide. While expectation of retarded hydrogen abstraction by intermediate radicals was rewarded and cyclization was favored under these conditions, more complex reaction products also resulted and the overall yield of volatile products decreased. Reactions with bis(trifluoromethyl) disulfide gave 12–15 volatile products in benzene, acetonitrile, or cyclohexane and the cyclization ratio, found after desul-

furization, was particularly low for the first two solvents. Irradiation of thiophenol, diphenyl disulfide, and geranyl acetate gave the acyclic adduct **18** in 42% yield.[29]

Reactions of the aromatic olefins **24–28** with ethanethiol and radical initiation by photolysis with diphenyl disulfide or by thermolysis of benzoyl peroxide and photolysis with dimethyl disulfide gave the acyclic adducts **29–33** in 50–83%

Scheme VII. Reactions of Arylalkenes with Thiyl Radicals



yields. The uncyclized products were identified by NMR spectra and their molecular ions. Cyclization products, if formed, were obscured in uncharacterized minor product mixtures (2–8%).

The present study shows that thiyl radical initiated cyclizations of dienes occur readily when unstrained cyclopentane products can be formed but that cyclization yields decrease in favor of formation of olefinic addition products when cyclizations are forced toward energetically less favored, strained or six-membered ring closure and that no significant cyclization arises from attack on an aromatic ring. Chain transfer (H transfer) is expected to be competitive in reactions of thiols with dienes. This process leads to more acyclic adducts as the energetic requirement for the cyclization increases. The chain transfer process is less competitive for the dialkyl disulfide reactions but products derived from alkyl hydrogen transfer then predominate. These results may be compared with those of benzoyloxy radical induced cyclizations of dienes and aryl olefins where the energetically more demanding cyclizations have been achieved. The difference in ease of such cyclizations initiated by thiyl vs. benzoyloxy radicals may lie in a decreased electrophilic reactivity of radicals generated with thioalkyl vs. benzoyloxy substituents on the adjacent carbon. However, most of the benzoyloxy radical initiated cyclizations were also obtained under conditions less favorable for hydrogen transfer.

Experimental Section

Reaction of Dimethyl Diallylmalonate with Ethanethiol. A. Diphenyl Disulfide Initiated Photolysis. A mixture of 122 mg (0.576 mmol) of dimethyl diallylmalonate, bp 120–122 °C (17 mm) (one VPC peak on column below), 2 mg (0.0092 mmol) of diphenyl disulfide, and 43 μL (35 mg, 0.57 mmol) of ethanethiol in a Pyrex tube was purged with nitrogen and sealed under a nitrogen atmosphere. The mixture was then irradiated for 15 h using a 450-W Hg high-pressure lamp. Distillation of the reaction mixture at 100–120 °C (0.03 mm) gave 105 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed some remaining starting material and three products with the following retention times and relative areas: starting material, 2.25 min (2.93); **3**, 20.5 min (1); **2b**, 23.5 min (1.18); **2a**, 28 min (7.15). The mixture was fractionated by preparative VPC on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column at 195 °C. Three fractions were collected corresponding to the three products listed above: **2a**, NMR ($CDCl_3$) δ 3.87 (s, 3 H), 1.4–2.7 (broad, complex pattern, 10 H), 1.28 (t, J = 7.5 Hz, 3 H), 0.9 (d, J = 7.5 Hz, 3 H), *m/e* 274 (M^+); **3**, *m/e* 274 (M^+); **2b**, *m/e* 274 (M^+). Irradiation of the same reactants for 68 h in 7 mL of benzene gave 96 mg of oil, distilled at 100–120 °C (0.03 mm), with VPC showing a trace of starting material and components **2a,b** with relative areas of 1 and 7.05. Reactions with 1.2 g of diallylmalonate and 10% excess of ethanethiol gave results shown in Table I.

B. Benzoyl Peroxide Initiated Thermolysis. A mixture of 116 mg (0.545 mmol) of dimethyl diallylmalonate, 3.4 mg (0.014 mmol) of benzoyl peroxide, and 35 μL (29 mg, 0.47 mmol) of ethanethiol was purged with nitrogen, sealed in a Pyrex tube, and then heated overnight in an oven at 85 °C. Distillation of the reaction mixture at 100–120 °C (0.03 mm) gave 102 mg of a clear liquid. VPC showed some remaining starting material and three products with retention times corresponding to those from the diphenyl disulfide initiated photolysis. Relative areas follow: starting material (5.95), **3** (1), **2b** (3.75), and **2a** (14.7).

A similar reaction in 7 mL of benzene gave 92 mg of oil, distilled at 100–120 °C (0.03 mm), with VPC showing mostly starting material with very small amounts (<1%) of two products, corresponding by VPC to those of the photolysis in benzene.

C. Uninitiated Reaction. A mixture of 127 mg (0.60 mmol) of dimethyl diallylmalonate and 44 μL (37 mg, 0.59 mmol) of ethanethiol was placed in a Pyrex tube, purged with nitrogen, sealed, and stored in the dark overnight. VPC of the reaction mixture showed starting material and three products corresponding to those seen in the photolytic reaction. Relative areas follow: starting material (3.96); **3** (1); **2b** (trace); **2a** (1.67).

Raney Nickel Desulfurization of the Dimethyl Diallylmalonate–Ethanethiol Adduct. The major product from the diphenyl disulfide initiated photolysis of ethanethiol and dimethyl diallylmalonate was treated with an excess of W4 Raney nickel in 5 mL of refluxing methanol for 24 h. The reaction mixture was filtered and the catalyst was triturated three times with 5-mL portions of boiling methanol. The methanol solution was concentrated to give a clear liquid which had only one component, **4a** by VPC (5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W at 195 °C): NMR ($CDCl_3$) δ 3.72 (s, 6 H), 1.8–2.6 (broad, complex pattern, 6 H), 0.87 (d, J = 7 Hz, 6 H). This compound corresponded to the *cis*-dimethylcyclopentane product obtained by the following alternative synthesis. Desulfurization of the entire product mixture obtained on photolysis with ethanethiol allowed matching with dimethyl dipropylmalonate[30] (**5**) and the *cis*- and *trans*-dimethylcyclopentanes **4a,b** by VPC on DEGS or Carbowax columns. No methylcyclohexane product could be seen.

Reaction of Dimethyl Diallylmalonate with Dimethyl Disulfide. Dimethyl diallylmalonate (0.114 g, 0.538 mmol) and dimethyl disulfide (47 μL, 0.53 mmol) were placed in a Pyrex tube, purged with nitrogen, and sealed. The mixture was then irradiated for 12 h using a 450-W high-pressure Hg lamp. Distillation of the reaction mixture at 100–130 °C (0.03 mm) gave 0.124 g of a clear, colorless liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed no starting material but two components with the following retention times and relative areas: A, 8.5 min (1); B, 10 min (11.7). This product was fractionated by preparative VPC on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column at 190 °C. The second fraction showed NMR ($CDCl_3$) δ 3.68 (s, 6 H), 1.9–2.6 (broad multiplet, 5 H), 2.08 (s, 3 H), 0.88 (d, J = 6 Hz, 3 H); *m/e* 260 (M^+, corresponds to dimethyl diallylmalonate plus methanethiol); small peaks were also seen at *m/e* 275, 291, and 306 (corresponding to 1:1 adduct).

Raney Nickel Desulfurization of Dimethyl Disulfide–Dimethyl Diallylmalonate Adduct. A sample of the products from the photolysis of dimethyl disulfide and dimethyl diallylmalonate was stirred with an excess of W4 Raney nickel for 5 h. The mixture was filtered and the catalyst was washed several times with boiling methanol. The combined methanol solutions were concentrated and distilled at 80–100 °C (0.03 mm) to give a clear, colorless liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 124 °C showed two peaks with retention times and rel-

ative areas of 8 min (1) and 10.5 min (4.58); NMR ($CDCl_3$) δ 3.72 (s, 6 H), 1.64–2.6 (broad pattern, 6 H), 0.88 (d, 6 H). The minor peak had the same VPC retention time as did methyl di-*n*-propylmalonate (**5**). The major peak had the same VPC retention time as the desulfurization product **4a** of the ethanethiol–dimethyl diallylmalonate reaction.

Reaction of Dimethyl Diallylmalonate with Bis(trifluoromethyl) Disulfide. A mixture of 0.545 g (2.57 mmol) of dimethyl diallylmalonate and 0.552 g (2.73 mmol) of bis(trifluoromethyl) disulfide was sealed in a Pyrex tube at 0.03 mm pressure and irradiated for 15 h using a 450-W high-pressure Hg lamp. Distillation of the reaction mixture at 100–130 °C (0.03 mm) gave 0.821 g of a pale yellow liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 180 °C showed 11 well-resolved components with the following retention times and relative areas: 1.375 min (0.071), 2 min (0.035), 2.5 min (0.19), 3.5 min (0.032), 4.25 min (0.38), 6.75 min (0.071), 8.75 min (1), 10.25 min (0.17), 18 min (0.11), 25.25 min (0.45), 31 min (0.42); *m/e* (rel intensity) 414 (4.1), 383 (6.9), 345 (18.5), 313 (27), 151 (39), 93 (54.7), 91 (54), 79 (47.5), 77 (39.7), 59 (100), 41 (53.4), 39 (39.7).

Raney Nickel Desulfurization of Dimethyl Diallylmalonate–Bis(trifluoromethyl) Disulfide Reaction Mixture. A solution of 266 mg of the product from the above photolysis in 5 mL of methanol was heated at reflux overnight with an excess of W4 Raney nickel. The mixture was filtered and the catalyst was washed several times with boiling methanol. Distillation at 80–100 °C (0.03 mm) gave 115 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 140 °C showed five peaks with retention times and relative areas of 3.5 min (1), 4.75 min (1.62), 6.5 min (3.22), 8.25 min (0.665), 26 min (0.464). The major (6.5 min) component was identical by VPC with **4a**. The first component (3.5 min) had a retention time the same as that of dimethyl di-*n*-propylmalonate (**5**).

Reaction of α-Acoradiene with Dimethyl Disulfide. A solution of 70 mg (0.34 mmol) of α-acoradiene[26] and 30 μL (32 mg, 0.34 mmol) of dimethyl disulfide in 3 mL of cyclohexane was sealed in a Pyrex tube at 0.03 mm pressure. The solution was irradiated for 15 h using a 450-W high-pressure mercury lamp. Concentration of the solution gave a pale yellow oil which was distilled at 100–130 °C (0.03 mm) to give 65 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed traces of acoradiene, one very minor component, and one major component with retention times and relative peak areas of 0.75 min (trace), 2.875 min (0.036), 5.75 min (1). A mass spectrum of the distilled product showed peaks at *m/e* (rel intensity) 298 (0.8), 252 (16), 250 (8), 191 (100), 135 (34), 109 (36), 95 (77), 81 (62), 69 (36), 55 (40), 41 (45).

Raney Nickel Desulfurization of the α-Acoradiene–Dimethyl Disulfide Product. The product from the photolysis of dimethyl disulfide and α-acoradiene in cyclohexane was stirred for 8 h with an excess of W4 Raney nickel in 5 mL of refluxing ethanol. The mixture was then filtered, the catalyst was washed with boiling ethanol, and the combined filtrates were concentrated and distilled at 70–90 °C (0.03 mm) to give 36 mg of a clear liquid: *m/e* (rel intensity) 206 (61), 95 (50), 93 (56), 82 (100), 81 (46), 69 (46), 55 (49), 41 (76); NMR ($CDCl_3$) δ 2.1–1.1 (m), 1.1–0.7 (m), both multiplets had approximately the same integration. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 120 °C showed only one peak with a retention time of 3.5 min, identical with that of dihydrocedrene and differing from those of tetrahydro-α-acoradienes in respective enrichment VPC analyses. Dihydrocedrene and the present reaction product showed identical IR spectra.

An analogous reaction sequence with photolysis of dimethyl disulfide and α-acoradiene in benzene and subsequent desulfurization again gave mostly dihydrocedrene and 15% of an unidentified compound with longer VPC retention time (5.75 min vs. 4 min).

Catalytic Hydrogenation of α-Acoradiene. A solution of 66 mg (0.32 mmol) of α-acoradiene in 5 mL of ethanol was stirred with 10 mg of 10% palladium on charcoal under 1 atm of hydrogen until the theoretical amount of hydrogen (15 mL) had been taken up. The reaction mixture was then filtered, concentrated, and distilled at 70–90 °C (0.03 mm) to give 54 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 120 °C showed two peaks with retention times and relative areas of 2.75 min (1) and 3.125 min (2.8).

Catalytic Hydrogenation of Cedrene. A solution of 55 mg (0.27 mmol) of cedrene in 2 mL of ethanol was shaken overnight with 10% palladium on charcoal under 40 psi of hydrogen. The mixture was filtered, concentrated, and distilled at 70–90 °C (0.03 mm) to give 45 mg of a clear liquid: *m/e* (rel intensity) 206 (67), 163 (47), 122 (38), 121 (37), 95 (38), 82 (100), 55 (38), 41 (64); NMR ($CDCl_3$) δ 2.2–1.2 (m), 1.2–0.72 (m) (the multiplets have approximately a 1:1 integration).

Reaction of Bulnesene with Dimethyl Disulfide. A solution of 0.397 g (1.94 mmol) of bulnesene[27] and 171 μL (183 mg, 1.94 mmol) of dimethyl disulfide in 10 mL of cyclohexane was sealed in a Pyrex tube at 0.03 mm pressure and irradiated for 24 h using a 450-W high-pressure mercury lamp. Concentration of the reaction mixture gave a yellow-brown oil which was distilled at 120–180 °C (0.03 mm) to give 0.307 g of a pale yellow oil. A VPC of this oil on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 192 °C showed eight peaks with retention times and relative areas of 1 min (1.0 bulnesene), 1.75 min (0.10), 1.875 min (0.15), 3.5 min (0.14), 4.625 min (0.14), 6.5 min (0.77, several components), 9.75 min (0.014), 12.25 min (0.051). Preparative TLC of this material on a 20 × 20 cm silica gel coated plate developed with hexane gave four fractions: I, R_f 0–0.1; II, R_f 0.1–0.3; III, R_f 0.3–0.5; IV, R_f 0.5–0.9. Three fractions were analyzed by VPC using a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C; fraction IV appeared to be almost pure bulnesene; fractions II and III were a mixture of products, including the major product, and appeared to be free of bulnesene; fraction I was mostly a product corresponding to the peaks with retention times of 1.75 or 1.875 min. Fractionation of fraction II by preparative VPC on a 10 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 180 °C gave a sample of the major product: *m/e* (rel intensity) 252 (75), 237 (37), 204 (100), 190 (59), 108 (45), 81 (45), 61 (46), 41 (48).

Raney Nickel Desulfurization of the Bulnesene–Dimethyl Disulfide Adduct. Fraction III from the preparative TLC of the bulnesene–dimethyl disulfide reaction mixture was stirred for 12 h with an excess of W4 Raney nickel in refluxing ethanol. The solution was filtered and the catalyst was washed several times with boiling ethanol. The combined filtrates were concentrated and distilled at 70–90 °C (0.03 mm) to give 21 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 120 °C showed five poorly resolved peaks with retention times and relative peak heights of 2 min (0.5, shoulder), 2.25 min (1), 2.5 min (0.3), 3 min (0.3), 3.75 min (0.3). This material was shaken overnight in 1 mL of ethanol with a catalytic amount of 10% palladium on charcoal under 40 psi of hydrogen. No change in the VPC of the material was observed after this treatment. Fractions 2 and 3 showed molecular ions of *m/e* 208 (tetrahydrobulnesene). Of fractions 4 and 5 with *m/e* 206 (dihydropatchulenes) the latter could be matched in mass fragmentation with a dihydro-α,γ-patchulene sample obtained by hydrogenation (below). A corresponding reaction sequence using benzene as photolysis solvent also gave these four product fractions in similar amounts in addition to two minor components.

Catalytic Hydrogenation of γ-, α-, and β-Patchulenes. A solution of 243 mg of the isomeric patchulenes (1:3.8:1.6)[27a] in 15 mL of ethanol was stirred with 17 mg of 10% palladium on charcoal under hydrogen until uptake ceased (34 mL). The mixture was then filtered and concentrated to give an oil which was distilled at 70–90 °C (0.03 mm) to give 199 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 130 °C showed three peaks with retention times and relative areas of 1.75 min (1) (γ-patchulene, unreduced), 3.375 min (2.52), and 4 min (1.96). Samples of each component were collected by preparative VPC on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column at 180 °C. The first fraction showed peaks at *m/e* (rel intensity) 218 (31) contaminant, 204 (71), 184 (100), 151 (90), 133 (35), 119 (51), 93 (32), and 41 (44); fraction 2 had peaks at *m/e* (rel intensity) 206 (100), 191 (74), 163 (79), 107 (62), 95 (61), 82 (79), 81 (60), 41 (56); fraction 3 had peaks at *m/e* (rel intensity) 206 (77), 163 (100), 122 (75), 107 (81), 95 (100), 81 (82), 69 (63), 41 (91).

Reaction of Geranyl Acetate with Ethanethiol. A. Diphenyl Disulfide Initiated Photolysis. A mixture of geranyl acetate, bp 63–70 °C (0.1 mm)[31] (1.97 g, 0.01 mol), ethanethiol (0.74 mL, 0.62 g, 0.01 mol), and diphenyl disulfide (0.024 g, 0.098 mmol) was purged with nitrogen and sealed in a Pyrex tube. The mixture was irradiated with a 450-W high-pressure Hg lamp for 15 h. Distillation of the mixture gave three fractions: 1, 1.03 g, bp 55–75 °C (0.03 mm); 2, 0.21 g, bp 75–93 °C (0.03 mm); 3, 0.79 g, bp 94–180 °C (0.03 mm). A VPC of fraction 3 on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed the presence of starting material, three major products, and three very minor products with retention times and relative areas of A, 1.5 min (0.30, starting material); B, 6 min (1.03); C, 7 min (1); D, 8.5 min (2.13); E, 9.5 min (0.05); F, 12 min (0.09); G, 14 min (0.092). This material was fractionated by preparative VPC on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column at 190 °C. Three fractions were collected, corresponding to B, C, and D listed above. B, **20**, *m/e* 258, 260; NMR ($CDCl_3$) δ 5.28 (t, J = 8 Hz, 1 H), 4.28 (q, J = 6 Hz), 2.8–2.3 (5-line pattern, J = 7 Hz,

overlapping a broad absorption), 3.2 and 3.22 (singlets on one finely split doublet), 1.8–1.1 (complex pattern), 1.0 (5-line pattern, J = 4 Hz). C, **19**, m/e 258, 260; NMR ($CDCl_3$) δ 5.58 (t, J = 8 Hz, 1 H), 4.78 (d, J = 8 Hz, 2 H), 2.76–2.2 (complex pattern, 4–5 H), 1.02 (doublet of doublets, J = 4 and 8 Hz, 6 H). D, 18, m/e 258; NMR ($CDCl_3$) δ 5.58 (t, J = 7 Hz, 1 H), 4.76 (d, J = 7 Hz, 2 H), 2.8–2.2 (complex pattern, 4–5 H), 2.12 (s, 3 H), 1.80 (s, 3 H), 1.28 (t, J = 7 Hz, 3–4 H), 1.01 (t, J = 6 Hz, 6 H). (Small m/e 260 peaks are due to contamination of geranyl acetate with small amounts of citronellyl acetate in this but not in subsequent experiments.)

An analogous reaction in 14 mL of benzene, purged with nitrogen, sealed in a Pyrex tube, and irradiated for 68 h gave 190 mg of a clear oil which by VPC appeared to be about 95% starting material, with about seven or eight products comprising the rest of the mixture.

B. Benzoyl Peroxide Initiated Thermolysis. A mixture of 107 mg (0.545 mmol) of geranyl acetate, 40 μL (33 mg, 0.54 mmol) of ethanethiol, and 3 mg (0.01 mmol) of diphenyl disulfide was purged with nitrogen and sealed in a Pyrex tube. The mixture was then heated in an oven at 85 °C for 15 h. Distillation of the mixture at 100–130 °C (0.03 mm) gave 98 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed the product to consist of about 92% starting material, with the remainder distributed approximately equally between four products with retention times of 4.75, 5.5, 6.75, and 8.5 min. A similar reaction in benzene gave 99% recovery of starting material.

Raney Nickel Desulfurization of Ethanethiol–Geranyl Acetate Reaction Mixture. The product from the diphenyl disulfide initiated photolysis of ethanethiol and geranyl acetate was fractionated by preparative VPC on a 10 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 170 °C. One fraction was collected which contained all of the adducts and none of the starting material. This material (36 mg) was heated overnight in refluxing ethanol with an excess of W4 Raney nickel. The reaction mixture was then filtered and the catalyst was washed several times with boiling ethanol. The filtrate was concentrated and distilled at 50–70 °C (0.03 mm). A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 127 °C showed two peaks with retention times and relative areas of 2.5 min (9.4) and 3.75 min (1). The major peak was identical by VPC with a sample of tetrahydrogeranyl acetate. The minor peak was identical by VPC with dihydrocyclogeranyl acetate.

Reaction of Geranyl Acetate with Dimethyl Disulfide. Geranyl acetate (1.96 g, 0.01 mmol) and dimethyl disulfide (0.88 mL, 0.94 g, 0.01 mol) were sealed in a Pyrex tube and irradiated for 17 h with 450-W high-pressure Hg lamp. The reaction mixture was then distilled and three fractions were collected: fraction 1, 0.52 g, bp 65–94 °C (0.08 mm); fraction 2, 1.06 g, bp 94–120 °C (0.08 mm); and fraction 3, 0.16 g, bp 120–160 °C (0.08 mm). Vapor phase chromatography using a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 185 °C showed fraction 1 to be mainly starting material with small amounts of three products. Fraction 2 consisted of starting material, three major products with retention times and relative areas of 0.75 min (2.26); **20**, 3.25 min (1.67); **19**, 3.75 min (1); **18**, 4.5 min (2.78); and three minor products with retention times of 5, 6, and 7 min. Accurate measurement of the areas of these last three peaks was not possible. Fraction 3 consisted of the same components as fraction 2 with one additional component having a retention time of 14.5 min. The approximate relative peak areas were 1.00, 0.08, 0.47, 1.05, 0.036, 0.16, and 1.33. A portion of fraction 2 was fractionated by preparative VPC on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column at 180 °C. Six fractions were collected. A: m/e 244 (M^+); NMR ($CDCl_3$) δ 4.9 (t), 4.1 (m), 2.1 (s), 2.025 (s), 2.02 (s). 2.01 (s), 1.82 (s), 1.62 (d), 1.41 (d), 0.92 (t). B: m/e 244 (M^+); NMR ($CDCl_3$) δ 5.25 (t, J = 7 Hz, 1 H), 4.5 (d, J = 7 Hz, 2 H), 2.24 (m, 3 H), 2.03 and 2.01 (s, 9 H), 1.74 (s, 3 H), 0.94 (doublet of doublets, J = 6 and 2 Hz, 6 H). C: m/e 244 (M^+); NMR ($CDCl_3$) δ 5.24 (t, J = 7 Hz, 1 H), 4.48 (d, J = 7 Hz, 2 H), 2.08–2.28 (m, 3 H), 2.04 (s, 8–9 H), 1.68 (s, 3–4 H), 0.96 (doublet of doublets, J = 8 and 4 Hz, 6 H). D, E, and F, m/e 244 (M^+). Not enough material was obtained for an NMR of D, E, or F.

Raney Nickel Desulfurization of Photolysis Product. Fraction 2 from the distillation of the above photolysis product was fractionated by preparative VPC on a 10 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 190 °C. Two fractions were collected, the first containing starting material and the second containing all of the products. A portion (92 mg) of the product fraction was heated in refluxing acetone for 6 h with an excess of W4 Raney nickel. The mixture was then filtered and the catalyst was washed several times with boiling acetone. The combined filtrates were concentrated on a rotary evaporator and distilled at 80–120 °C (0.03 mm) to give 55 mg of a clear, colorless liquid. This liquid was stirred in 10 mL of acetic acid with 6 mg of 10% palladium on charcoal under 1 atm of hydrogen until hydrogen uptake ceased. The mixture was then filtered, concentrated, and distilled to give 10 mg of a clear, colorless liquid: IR (liquid film) 3450 (m, broad), 2850–3000 (s), 1740 (s), 1700 (m, sh), 1350–1380 (m, b), 1200–1275 cm^{-1} (m). This liquid was heated at 90 °C with acetic anhydride and potassium carbonate in a sealed tube overnight. After cooling, the mixture was dissolved in benzene and washed with saturated sodium bicarbonate and saturated brine, dried ($MgSO_4$), and distilled at 80–120 °C (0.03 mm) to give 8.9 mg of a clear liquid. A VPC of this material on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 125 °C showed four peaks with retention times and relative areas for tetrahydrogeranyl acetate (**23**), 3.25 min (5.5); the epimeric dihydrocyclogeranyl acetates (**22**), 4 min (1), 4.5 min (0.16), and a peak at 6 min (0.07).

Reaction of Geranyl Acetate and Dimethyl Disulfide in Cyclohexane. Irradiation of geranyl acetate (0.49 g, 2.5 mmol), dimethyl disulfide (0.21 mL, 0.24 g, 2.5 mmol), and 5 mL of cyclohexane for 24 h, concentration, and distillation at 100–150 °C (0.025 mm) gave 0.273 g of a clear liquid and 0.351 g of a nonvolatile material. A VPC of the distillate on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 190 °C showed, in addition to a small trace of starting material, seven components with the following retention times and relative peak areas: starting material, 0.75 min (1); A, 3.25 min (6.92); B, 3.75 min (4.95); C, 4.5 min (5.39); D, 5.25 min (1.15); E, 5.75 min (1.24); F, 6.625 min (1.91); G, 14.5 min (17.75). This product mixture was fractionated by preparative VPC on a 10 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 190 °C into 49.1 mg of components A–F, m/e 244 (M^+), and 108 mg of component G, m/e 290 and 292, corresponding to geranyl acetate plus dimethyl disulfide and geranyl acetate plus two molecules of methyl mercaptan: NMR ($CDCl_3$) δ 4.28 (d, J = 6 Hz, overlapping with another absorption), 2.74 (m), 2.16 (s), 2.08 (s), 1.76 (broad), 1.54 (broad), 1.25 (s), 0.98 (symmetrical multiplet). A reaction in benzene gave analogous results.

Raney Nickel Desulfurization of Photolysis Product. Components A–F from the preparative VPC of the distilled photolysis product were stirred in 5 mL of refluxing ethanol with an excess of W4 Raney nickel for 6 h. The mixture was then filtered and the catalyst washed with several portions of boiling ethanol. The resulting ethanol solution was concentrated on a rotary evaporator and distilled at 80–100 °C (0.03 mm) to give 32.1 mg of a clear, colorless liquid. A VPC of this material on a 5 ft × 0.125 in. 10% Carbowax 20M column at 125 °C showed four components with retention times and relative areas of 3 min (1), tetrahydrogeranyl acetate 3.75 min (1.78), and 4.25 min (0.05), dihydrocyclogeranyl acetate, and a peak at 5.375 min (0.13).

Component G from the preparative VPC of the photolysis product was similarly treated. Distillation gave 7 mg of a clear, colorless liquid. A VPC showed three components with retention times and relative areas of 1.75 min (1), 3 min (3.08), tetrahydrogeranyl acetate, 4.75 min (0.103).

Reaction of Geranyl Acetate with Diphenyl Disulfide. Photolysis in Acetonitrile. A solution of 1.97 g (0.011 mol) of geranyl acetate and 2.18 g (0.01 mol) of diphenyl disulfide in 160 mL of acetonitrile was purged with nitrogen and irradiated with a Hg high-pressure lamp through a Vycor filter for 24 h. The light immersion well became heavily coated with an ether- and acetone-insoluble material. The solution was concentrated and distilled to give two fractions: A, 1.99 g, bp 70–95 ° C (0.1 mm); B, 0.75 g, bp 95–250 °C (0.1 mm). Some nonvolatile material remained. A VPC of fraction B on a 5 ft × 0.125 in. 5% SE-30 on Chromosorb W column at 210 °C showed, in addition to a small amount of starting material, seven components with the following retention times and relative areas: 0.75 min (0.11), 1.25 min (0.08), 1.5 min (3.49), 1.75 min (0.36), 5.5 min (1.84), 10.5 min (6.5), 13 min (1). Fraction B was fractionated by preparative VPC on a 10 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 220 °C. Five fractions were collected: 1, NMR ($CDCl_3$) δ 7.6 (d, J = 8 Hz), 7.35 (d, J = 7 Hz), 4.63 (d, J = 8 Hz), 2.7 (s), 1.64 (d, J = 9 Hz), 0.9 (broad); 2, m/e (rel intensity) 294 (2.6), 218 (3.2), 186 (100), 185 (41), 184 (19), 140 (2), 109 (13); NMR ($CDCl_3$) δ 7.38 (s), 2.28, 2.07, 1.8, 1.24, 0.9 (broad, weak absorptions); 3, m/e (rel intensity) 294 (4.8), 285 (1), 218 (100), 185 (37), 184 (65), 140 (67), 109 (28); NMR ($CDCl_3$) δ 7.3 (m), 4.26 (broad), 3.28 (broad), 2.04 (weak, broad), 1.64 (s), 1.2 (s), 0.9 (weak, broad); 4, m/e (rel intensity) 294 (28), 255 (13), 218 (69), 185 (36), 184 (56), 140 (44), 109 (100); NMR ($CDCl_3$) δ 7.3 (m, strong), 3.3 (broadened singlet), 1.65 (s), 1.28 (s), 0.9 (m, broad); 5, m/e (rel intensity) 294 (100), 285 (1.4), 218 (21), 185 (42), 184 (76), 140 (15), 109 (64); NMR ($CDCl_3$) δ 7.39 (m), weak absorptions at 4.27 (s), 3.3 (broadened singlet), 1.64 (s), 1.26 (s, broad), 0.9 (m, broad); IR ($CHCl_3$) 2910 (m, broad), 1565 (m-s), 1435 (sharp), 1475 cm^{-1} (sharp).

Raney Nickel Desulfurization of Photolysis Product. Fraction

B (68.5 mg) from the distillation of the crude photolysis product was treated with an excess of W4 Raney nickel in refluxing ethanol for 4 h. Distillation of the product at 100 °C (0.03 mm) gave 10.3 mg of a clear liquid: IR (thin film) 3400 (m, broad), 3070 (w, sh), 3035 (w, sh), 2960 (s, sh), 2935 (s, sh), 2860 (m, sh), 2810 (shoulder), 1730 (m, sh), 1450 (m, broad), 1365 (m, broad), 1235 (m, broad), 1050 cm^{-1} (m, broad). This liquid was added to acetic anhydride (10 μL) and a few crystals of anhydrous sodium acetate in a Pyrex tube which was sealed and heated in an oven at 110 °C for 6 h. Distillation at 100 °C (0.03 mm) gave 5.2 mg of a clear liquid. A VPC of this liquid on a 5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W column at 125 °C showed six peaks with the following retention times and relative areas: A, 3 min (1), B, 4 min (0.078), C, 5 min (1.76), D, 7 min (0.167), E, 8.25 min (5.34), F, 21.5 min (2.22). A VPC of a mixture of this product and tetrahydrogeranyl acetate showed enhancement of component A. A VPC of the product with added dihydrocyclogeranyl acetate showed enhancement of components B and C.

Analogous cyclization reactions and desulfurizations were carried out in benzene and cyclohexane with diphenyl disulfide and with trifluoromethyl disulfide and di-*tert*-butyl disulfide. The results are listed in Table II.

Preparation of Dihydrocyclogeranyl Acetate (22). α-Cyclogeraniol[32] (1.014 g, 6.6 mmol) and 70 mg of 10% palladium on charcoal were stirred in 20 mL of ethanol under 1 atm of hydrogen until the calculated amount of hydrogen (148 mL) had been absorbed. The mixture was then filtered, concentrated, and distilled to give 0.433 g (42%) of dihydrocyclogeraniol distilled at 80–100 °C (block temperature) at 0.04 mm: NMR ($CDCl_3$) δ 3.76 (d, J = 6 Hz), 2.0 (broad singlet), 1.68–1.08 (complex pattern), 1.0 (s), 0.88 (s).

Dihydrocyclogeraniol (0.119 g, 0.767 mmol), acetic anhydride (72.3 μL, 0.0782 g, 0.767 mmol), and sodium acetate (85.2 mg, 1.04 mmol) were heated in a sealed tube for 4 h at 150 °C. The tube was then cooled and the contents added to cold water. After standing for 15 min, the mixture was extracted several times with ether. The ethereal solutions were combined, washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried ($MgSO_4$), concentrated, and distilled at 80–100 °C (0.04 mm) to give 105.6 mg (69%) of a clear oil: NMR ($CDCl_3$) δ 4.04 (d, J = 4 Hz, 2 H), 1.98 (s, 3 H), 1.8–1.1 (complex pattern, 8 H), 1.0–0.8 (complex pattern, 9 H); IR (thin film), 1735 cm^{-1}; VPC (5 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W, 125 °C), 4 min (1) and 4.5 min (0.65).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; O, 16.14. Found: C, 72.96; H, 11.30.

1,1-Dicarbomethoxy-3-methylcyclohexane (6). Following a procedure developed in our laboratory by Reider for an analogous compound, a solution of 3.0 g (2.0 mmol) of methoxymethyl dimethylmalonate and 2.2 g (2.0 mmol) of *N*-pyrrolidino-1-propene in 10 mL of acetonitrile was stirred under nitrogen at room temperature for 20 h. Then 3 mL of acetic acid in 12 mL of water was added and after 5 h the mixture was extracted with dichloromethane and concentrated. Distillation at 95–110 °C (0.003 mm) gave 2.0 g of crude 4,4-dicarbomethoxy-2-methylbutyraldehyde. A solution of 0.90 g (5.0 mmol) of this compound in 6 mL of dry tetrahydrofuran was added over 1 h to a stirred suspension of 2.0 g (5.4 mmol) of triphenylvinylphosphonium bromide and 0.14 g (6.0 mmol) of sodium hydride in 4 mL of tetrahydrofuran. After stirring for 20 h the mixture was filtered through Celite and concentrated and the residue triturated with five 30-mL portions of hexane. Concentration and distillation at 120–130 °C (18 mm) gave 0.24 g of 4,4-dicarbomethoxy-6-methylcyclohexene: NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.5–3.0 (m, 5 H), 3.80 (s, 6 H), 5.7 (m, 2 H); *m/e* (rel intensity) 212 (7), 211 (58), 151 (81), 136 (68), 92 (89), 91 (96), 90 (100), 78 (84), 58 (75).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.70.

Catalytic hydrogenation of 0.10 g of the cyclohexene diester in 3 mL of methanol with 0.14 g of 5% palladium on charcoal catalyst resulted in 11 mL uptake of hydrogen in 10 min. Distillation of the product at 120–140 °C (18 mm) gave 0.10 g of **6** which showed only one VPC peak on a DEGS on Chromosorb W 13-ft column at 160 °C with retention time at 7.7 min (as compared with 7.1 min for the *meso*-dimethylcyclopentane diester **4a**) and *m/e* (rel intensity) 214 (0.6), 213 (4), 153 (21), 144 (100), 113 (51), 95 (100), 82 (43), 59 (21), 55 (21), 42 (28).

1,1-Dicarbomethoxy-3,4-dimethylcyclopentanes (4a,b). To a mixture of 0.22 g (0.91 mmol) of *meso*- or *dl*-1,4-dibromo-2,3-dimethylbutane and 0.12 g (0.92 mmol) of dimethyl malonate in 5 mL of refluxing methanol was added 0.11 g (2.0 mmol) of sodium methoxide in 10 mL of methanol, over 1.5 h. After an additional 1.5 h at reflux the solvent was evaporated under vacuum and the product dissolved in ether. Concentration and distillation at 120–140 °C (18 mm) gave 50 mg of product with the meso or *dl* compounds **4a,b** in respective experiments showing VPC peaks at 7.0 and 5.5 min on a 5-ft 20% Carbowax 20M on Chromosorb W column at 175 °C (15 mL/min) or at 7.1 and 5.8 min on a 13-ft DEGS on Chromosorb W column at 160 °C (25 mL/min): *m/e* 214; NMR ($CDCl_3$) δ 3.7 (s, 6 H), 1.6–2.6 (b, 6 H), 0.85 (d, 6 H) for cis dimethyl compound **4a** and 0.94 (d, 6 H) for trans dimethyl compound **4b**. In addition two compounds with shorter VPC retentions and solid products (2:1 alkylation) were found.

Preparation of Methyl 2-Phenylpent-4-enoate (25). Methyl phenylacetate (6.0 g, 0.04 mol) was added dropwise to a solution of triphenylmethylpotassium prepared from 9.76 g (0.04 mol) of triphenylmethane, 1.56 g (0.04 g-atom) of potassium, 35 mL of 1,2-dimethoxyethane, and 3 mL of butadiene.[33] To the resulting suspension was added 4.84 g (0.04 mol) of allyl bromide in 5 mL of 1,2-dimethoxyethane. After stirring for 1 h, the mixture was filtered and the residual potassium bromide was washed with ether. The combined organic solution was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to a yellow semisolid material. Distillation gave 6.50 g [bp 110–204 °C (14 mm)]. The distillate was chromatographed on silica gel using first hexane and then methanol as the eluent. The methanol fraction was concentrated and distilled to give 5.50 g (73.3%) of a clear liquid: bp 66–67 °C (0.25 mm); NMR ($CDCl_3$) δ 7.14 (s, 5 H), 5.8–5.4 (m, 1 H), 5.08–4.8 (m, 2 H), 3.56 (s, 3 H, overlapping with a triplet, 1 H), 2.9–2.3 (m, 3 H); IR (liquid film) 3080 (w), 3020 (w), 3000 (w), 2955 (w-m), 1730 (s) 1635 (m), 1600 cm^{-1} (m-w).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; O, 16.82. Found: C, 75.76; H, 7.48.

Preparation of Methyl 2-Phenyl-5-methyl-4-hexenoate (24). Using the preceding procedure and 7.64 g (31.3 mmol) of triphenylmethane, 1.22 g (0.0313 g-atom) of potassium, 35 mL of 1,2-dimethoxyethane, 2 mL of butadiene, 4.69 g (31.3 mmol) of methyl phenylacetate, and 1-bromo-3-methyl-2-butene (4.69 g, 31. mmol), gave 4.85 g (71%) of a clear, colorless, chromatographed liquid: bp 79–80 °C (0.025 mm); NMR ($CDCl_3$) δ 7.14 (s, 5 H), 4.94 (t, J = 6 Hz, 1 H), 3.56 (s, 3 H), 3.48 (t, J = 8 Hz, 1 H), 1.6 (s, 3 H), 1.54 (s, 3 H); IR (liquid film) 3020, 2960, 2950, 2910, 1735, 1600 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66. Found: C, 76.90; H, 8.42.

Preparation of 2-Phenyl-5-methyl-4-hexenonitrile. A solution of 6.0 g (0.05 mol) of phenylacetonitrile and 11.20 g (0.075 mol) of 1-bromo-3-methyl-2-butene in 5 mL of dimethyl sulfoxide and 20 g of a 50% aqueous sodium hydroxide solution were simultaneously added slowly to 40 mL of dimethyl sulfoxide in a 250-mL flask. Stirring was continued for 1 h after which the reaction mixture was diluted with 100 mL of water and extracted with two 40-mL portions of benzene and one 40-mL portion of ether. The combined organic solution was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated. Distillation of the residual oil gave three fractions: fraction 1, 1.13 g, bp 65–85 °C (0.05 mm); fraction 2, 5.21 g, bp 85–115 °C (0.05 mm); NMR ($CDCl_3$) δ 7.16 (s, 5 H), 5.04 (t, J = 8 Hz, 1 H), 3.66 (t, J = 6 Hz), 2.50 (t, J = 6 Hz), 1.66 (s, 3 H), 1.48 (s, 3 H); fraction 3, 2.47 g, bp 115–140 °C (0.05 mm) (contains dialkylated product).

Preparation of 2,5-Dimethyl-2-phenyl-4-hexenonitrile (26). A solution of 2-phenyl-5-methyl-4-hexenonitrile (2.70 g, 0.0146 mol) and methyl iodide (10.35 g, 0.073 mol) in 3 mL of dimethyl sulfoxide and 5.84 g of a 50% aqueous sodium hydroxide solution were simultaneously added to 12 mL of dimethyl sulfoxide. Stirring was continued for 1 h after which the reaction mixture was diluted with 40 mL of water and extracted with two 20-mL portions of benzene and one 20-mL portion of ether. The combined organic solution was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and dried ($MgSO_4$), concentrated, and distilled to give 2.23 g (77.5%) of a clear liquid: bp 78–90 °C (0.04 mm); NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.02 (t, J = 7 Hz, 1 H), 2.52 (d, J = 7 Hz), 1.66 (s, 6 H), 1.52 (s, 3 H); IR (thin film) 3060 (w), 2980 (m), 2235 (w), 1600 cm^{-1} (w).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.41; H, 8.55; N, 6.89.

Preparation of 2-Phenyl-5-hexenonitrile. Following the above procedure for 2-phenyl-5-methyl-4-hexenonitrile, a mixture of phenylacetonitrile (6.0 g, 0.05 mol) and 1-bromo-3-butene (10.13 g, 0.075 mol) in 5 mL of dimethyl sulfoxide and 20 g of 50% aqueous sodium hydroxide gave fraction 1, 1.37 g, bp 30–136 °C (8 mm); fraction 2, 5.31 g, bp 136–147 °C (8 mm); NMR ($CDCl_3$) δ 7.12 (s, 5 H), 5.8–5.3 (m, 1 H), 5.0 (d, J = 6 Hz, 1 H), 4.88 (s, 1 H), 3.70 (t, J = 8 Hz, 1 H), 2.3–1.8 (m, 4 H); fraction 3, 1.18 g, bp 147–155 °C (8 mm).

Preparation of 2-Methyl-2-phenyl-5-hexenonitrile (28). A mixture of 2-phenyl-5-hexenonitrile (5.31 g, 0.031 mol) and methyl iodide (6.6 g, 0.0465 mol) in 5 mL of dimethyl sulfoxide, and 12.4 g of a 50% aqueous sodium hydroxide solution, by the preceding procedure, gave 5.25 g (91%) of a clear liquid: bp 59–69 °C (0.03 mm); NMR ($CDCl_3$) δ 7.14 (m, 5 H), 5.76–5.36 (m, 1 H), 4.88 (d, J = 6 Hz, 1 H), 4.74 (s, 1 H), 1.96 (m, 4 H), 1.66 (s, 3 H); IR (liquid film) 3060 (m), 2980 (m), 2935 (m), 2235 (w), 1640 (w-m), 1600 cm^{-1} (w). Preparative VPC on a 10 ft × 0.375 in. SE-30 on Chromosorbe W column at 190 °C afforded the analytical sample.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.47; H, 8.23; N, 7.38.

Attempted Aryl Olefin Cyclizations. The preceding compounds (**24–28**) were subjected to reactions with ethanethiol with radical initiation by photolysis of diphenyl disulfide or thermolysis of benzoyl peroxide in benzene, or without solvent, in each case. Alternatively, dimethyl disulfide or di-*tert*-butyl disulfide were used as thiyl precursors. Procedures analogous to those used for the dienes, or reaction times extended to 4 days, led to olefin addition products and no significant cyclization. Crude and fractionated reaction products and Raney nickel desulfurized, hydrogenated products were examined by mass fragmentation, using characteristic m/e = M of aryl olefin + RS − H and m/e = M of aryl olefin, respectively, to find cyclization products.

Since no significant product fractions with such molecular ions were found but instead only products with m/e = M + RSH and m/e = M + 2 were obtained for the thiol adducts and their desulfurization products, experimental descriptions of these cyclization failures are omitted.

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Registry No.—**1**, 35357-77-8; **2a** (R′ = Et; A = H), 61558-92-7; **2a** (R′ = Me; A = SMe), 61558-93-8; **2a** (R′ = Me; A = H), 61559-00-0; **2b** (R′ = Et; A = H), 61558-94-9; **3** (R′ = Et; A = H), 61558-95-0; **3** (R′ = Me; A = SMe), 61558-96-1; **4a**, 61558-97-2; **4b**, 61558-98-3; **5**, 16644-05-6; **6**, 61558-99-4; **7**, 24048-44-0; **8** (X = H), 61559-01-1; **8** (X = SMe), 61559-02-2; **9**, 13567-54-9; **9** dehydro derivative, 546-28-1; **10**, 3691-11-0; **10** CH_3SSCH_3 adduct 1, 61559-32-8; **10** CH_3SSCH_3 adduct 2, 61559-03-3; **11**, 21073-70-1; **12a**, 25491-20-7; **12b**, 3724-42-3; **13a**, 560-32-7; **13b**, 508-55-4; **15**, 514-51-2; **16**, 105-87-3; **17** (R = Et), 61559-04-4; **17** (R = Me), 61559-05-5; **17** (R = Ph), 61559-06-6; **18** (R = Et), 61559-07-7; **18** (R = Me), 61559-08-8; **18** (R = Ph), 61559-09-9; **19** (R = Et), 61559-10-2; **19** (R = Me), 61559-11-3; **19** (R = Ph), 61559-12-4; **20** (R = Et), 61559-13-5; **20** (R = Me), 61559-14-6; **20** (R = Ph), 61559-15-7; **21** (R = Et), 61559-16-8; **21** (R = Me), 61559-17-9; **21** (R = Ph), 61559-18-0; **22**, 61559-19-1; **22** free alcohol, 34026-01-2; **23**, 20780-49-8; **24**, 61559-20-4; **25**, 14815-73-7; **26**, 51559-21-5; **28**, 61559-22-6; ethanethiol, 75-08-1; dimethyl disulfide, 624-92-0; bis(trifluoromethyl) disulfide, 372-64-5; diphenyl disulfide, 882-33-7; methyl iodide, 74-88-4; di-*tert*-butyl disulfide, 110-06-5; methoxymethyl dimethylmalonate, 61559-23-7; *N*-pyrrolidino-1-propene, 13937-88-7; 4,4-dicarbomethoxy-2-methylbutyraldehyde, 61559-24-8; triphenylvinylphosphonium bromide, 5044-52-0; 4,4-dicarbomethoxy-6-methylcyclohexene, 61559-25-9; *meso*-1,4-dibromo-2,3-dimethylbutane, 59635-00-6; *dl*-1,4-dibromo-2,3-dimethylbutene, 59634-99-0; dimethyl malonate, 108-59-8; methyl phenylacetate, 101-41-7; triphenylmethylpotassium, 1528-27-4; butadiene, 106-99-0; allyl bromide, 106-95-6; 1-bromo-3-methyl-2-butene 870-63-3; phenylacetonitrile, 140-29-4; 2-phenyl-5-methyl-4-hexenonitrile, 38179-48-5; 2-phenyl-5-hexenonitrile, 61559-26-0; 1-bromo-3-butene, 5162-44-7.

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(26) We thank Dr. B. Tomita of the University of Tokyo for generously providing a sample of α-acoradiene for this purpose. Dr. Tomita has previously studied the acid-catalyzed cyclization of acoradiene.
(27) Samples of bulnesene and patchouli alcohol were provided by Dr. T. A. Narwid of Hoffmann-La Roche, Inc., Nutley, N.J., and a sample of bulnesol was furnished by Dr. W. I. Taylor of International Flavors and Fragrances, Union Beach, N.J. The isomeric patchulenes were prepared from these compounds according to reported methods: (a) G. Buchi, R. E. Erickson, and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961); (b) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961); (c) R. B. Bates and R. C. Slagel, *J. Am. Chem. Soc.*, **84**, 1307 (1962).
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Ion Radicals. 39. Reactions of 10-Methyl- and 10-Phenylphenothiazine Cation Radical Perchlorates with Ketones[1,2]

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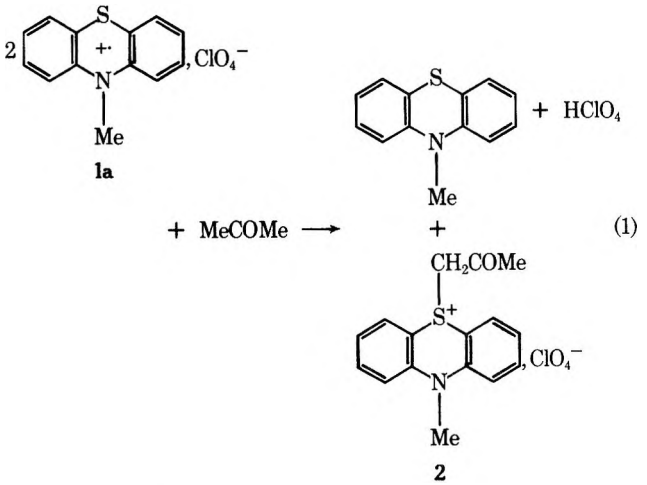
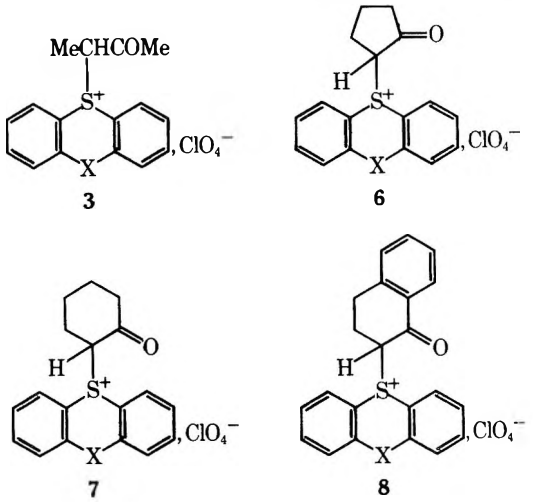
Reactions of 10-methyl- (**1a**) and 10-phenylphenothiazine cation radical perchlorate (**1b**) with butanone, cyclopentanone, cyclohexanone, and tetralone-1 led to ketoalkyl sulfonium perchlorates in which substitution at the α position of the ketones had occurred. Similar reactions were carried out between **1a** and methyl isopropyl ketone, acetophenone, and indanone-1. Several of the sulfonium salts were converted into the corresponding ylides by treatment with base. Reaction of 5-(2-indan-1-onyl)-5,5-dihydro-10-methylphenothiazine perchlorate (obtained from **1a** and indanone-1) with nucleophiles gave good yields of 2-substituted indanones.

We have earlier reported that the cation radicals of thianthrene and phenoxathiin react with dialkyl and alkylaryl ketones to give β-ketoalkylsulfonium salts.[5] Analogous reactions of 10-methyl- (**1a**) and 10-phenylphenothiazine cation radical (**1b**) have been carried out and are reported here. Although they gave for the most part reasonably good yields of sulfonium salts the reactions were rather slow. In our earlier work with the cation radicals of thianthrene (**1c**) and phenoxathiin (**1d**) the reactions were sufficiently facile to occur in acetonitrile solution. In the present work it was necessary in all but one case to use the ketone as the solvent, and even in that way reactions sometimes took several days. The stoichiometry of the reactions is illustrated in eq 1. Reactions of **1a** and **1b** with



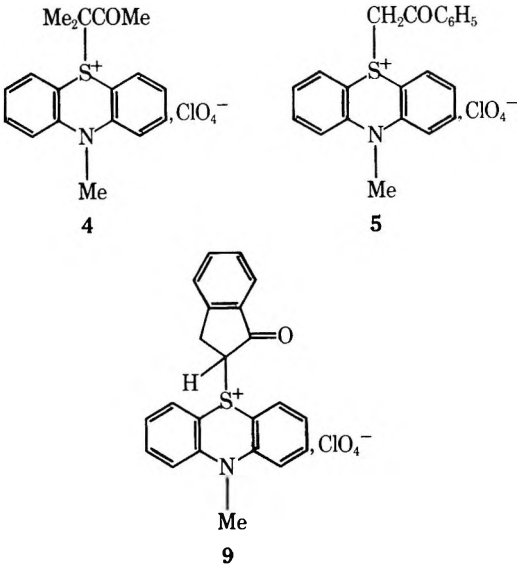
(1)

butanone, cyclopentanone, cyclohexanone, and tetralone-1 gave the products **3, 6, 7,** and **8,** while reactions of **1a** with

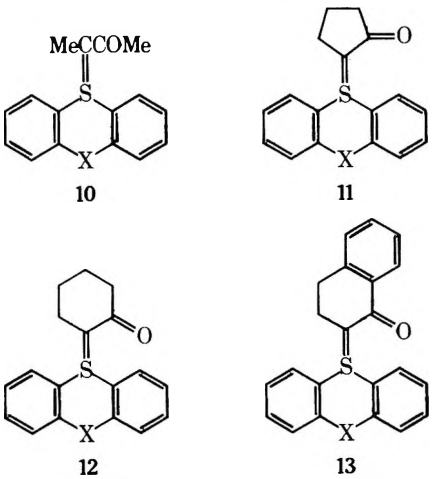


a, X = *N*-Me; **b**, X = *N*-Ph

methyl isopropyl ketone, acetophenone, and indanone-1 gave **4, 5** and **9,** respectively. Each product was characterized by elemental analysis[6] (except **9**) and NMR spectroscopy. Product **9** was further characterized by its reactions with nucleophiles, described below.



Several of the sulfonium salts were converted into the corresponding ylides by treatment with an alkylamine in solution. Each ylide (**10, 11, 12, 13**) was characterized by NMR and parent-peak mass spectrum or analysis.



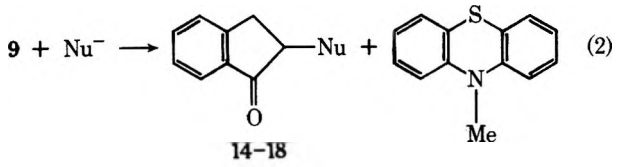
10–12, X = *N*-Ph; **13a**, X = N-Me; **13b**, X = N-Ph

Compound **9** was used for displacement reactions with nucleophiles (eq 2), and gave a series of substituted indanones (**14–18**) whose NMR spectra showed well-defined couplings

Table I. Chemical Shifts and Coupling Constants of Keto-Ring Protons in Substituted Indanones[a]

Registry no.	Compd	δ_A	δ_B	δ_C	J_{BA}[b]	J_{CA}[b]	J_{BC}[b]	Solvent
61723-05-5	14[c]	4.14	3.84	3.30	8.0	4.0	18.0	$CDCl_3$
61723-06-6	15[d]	4.29	3.51	3.83	8.0	3.5	18.0	$CDCl_3$
61723-07-7	16[e]	4.39	3.88	3.32	8.0	5.0	18.0	$CDCl_3$
1775-27-5	17[f]	4.74	3.85	3.32	7.0	3.5	18.0	CD_3CN
61723-09-9	18[g]	5.78	4.16	3.65	8.0	6.0	17.5	CD_3CN
61723-11-3	9	4.64	*h*	*h*	7.0	4.5	*h*	CD_3CN

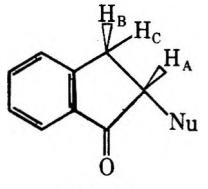
[a] A Varian XL-100 NMR instrument was used. [b] In hertz. Each proton, H_A, H_B, H_C, appeared as two well-defined doublets. [c] Aromatic protons, m, 4 H, δ 7.84–7.38. [d] Aromatic protons, m, 8 H, δ 7.87–7.33; Me, s, δ 2.45. [e] Aromatic protons, m, 4 H, δ 7.90–7.30; CH_2, q, δ 4.58, J = 7.0 Hz; Me, t, δ 1.20, J = 7.0 Hz. [f] Aromatic protons, m, 4 H, δ 7.78–7.36; lit.[7] values: δ H_A, H_B, H_C 4.65, 3.84, 3.42; J_{BA}, J_{CA}, J_{BC} 7.3, 3.5, and 18.5 Hz in $CDCl_3$. [g] (As the ClO_4^- salt) aromatic protons, m, 4 H, δ 7.96–7.52; pyridine protons, *o*-, d, δ, 8.78, J_{om} 6 Hz; *m*-, t, δ 8.12, $J_{m(o,p)}$ = 7 Hz; *p*-, t, δ 8.64, $J_{p,m}$ = 7 Hz. [h] Multiplets obscured by overlap with *N*-Me signal, s, δ 3.56; aromatic protons, m, 12 H, δ 8.02–7.28.



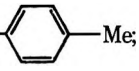
(2)

14–18

among the keto-ring protons. These couplings are given in Table I. In all cases, except **15**, the chemical shift of H_B is larger than that of H_C. A curious inversion of positions occurs in **15** in which H_B (characterized by the larger coupling J_{BA} = 8 Hz) appears at higher field than H_C, indicating the probable shielding effect of the tolyl ring on protons H_B and H_C in **15**. The assignments of coupling constants are made on the basis of the larger couplings being expected for cis protons (H_A and H_B) and are in accord with data reported by Jackson et al. for **17**.[7]



14–18

14, Nu = SCN; 15, Nu = O_2S—  —Me;

16, Nu = —S—C(=S)—OEt; 17, Nu = Br; 18, Nu = 

The reactions of **1a** and **1b** with butanone and of **1a** with methyl isopropyl ketone gave sulfonium salts (**3** and **4**) in which substitution had occurred at the branched α-carbon atom rather than at the α-methyl group. Analogous reactions were reported with thianthrene and phenoxathiin cation radicals (**1c** and **1d**).[5] These modes of substitution are consistent with the view[8] that the reaction involves electrophilic addition to the enol. Substitutions at the α-carbon atoms of unsymmetrical ketones, e.g., halogenations, which have been shown to involve the enol, also occur at the more substituted carbon atom, the controlling factor being addition to the more stable enol when a choice is available.[9,10]

The reactions of **1a** and **1b** with ketones are slower than the corresponding reactions of thianthrene and phenoxathiin cation radicals (**1c** and **1d**). Rates of reaction were not measured but it was found that whereas solutions of ketones and **1c** or **1d** in acetonitrile reacted readily, the reactions of similar solutions of **1a** and **1b** were very slow, so much so that ketones were themselves used as solvents for reactions of **1a** and **1b**. Quantitative rate comparisons are to be made. Differences in rates may be attributed at this stage to differences in positive charge density at the sulfur atom in the several cation radicals.

There is a statistical advantage of two sulfur atoms in **1c**, while in the other cation radicals positive charge density is also localized at atoms (nitrogen and oxygen) where reaction with the ketones cannot be fruitful. In accordance with this idea, HMO calculations of comparative charge densities in the cation radicals **1a–d** have shown that these decrease at the sulfur atom in the order **1c**, **1d**, **1a** ≃ **1b**.[11]

Experimental Section

10-Methyl- (**1a**) and 10-phenylphenothiazine cation radical perchlorates (**1b**) were prepared and assayed as described earlier.[12]

Reaction of 1a with Acetone. Formation of 2. A solution of 644 mg (2.06 mmol) of **1a** in 40 mL of acetone was stirred for 48 h. The dark green solution was concentrated on the aspirator, and the residue taken up in CH_2Cl_2. Ether was added to precipitate 100 mg (0.27 mmol, 26%) of crude **2**. Decolorization with charcoal and crystallization from CH_2Cl_2–ether gave a cream-colored solid: mp 161–163 °C dec; λ_{max} (CH_3CN) (10^{-3} ϵ) 320 nm (6.3), 269 (8.9), 253 (8.0), 219 (38.0); ^1H NMR (Me_2SO-d_6) δ 8.00–7.34 (m, 8 H, aromatic), 4.79 (s, 2 H, $-CH_2-$), 3.74 (s, 3 H, 10-CH_3), 2.12 (s, 3 H, CH_3). Addition of D_2O caused the disappearance of the singlet at δ 4.79.

Anal. Calcd for $C_{16}H_{16}NSClO_5$: C, 52.0; H, 4.36; N, 3.79; S, 8.66; Cl, 9.59. Found: C, 52.2; H, 4.65; N, 4.09; S, 8.81; Cl, 9.44.

The ether filtrate from crude **2** was concentrated and chromatographed on a silica gel (Merck 30-70 ASTM mesh) column. Elution with CCl_4 gave 300 mg (1.41 mmol, 137%) of crude 10-methylphenothiazine.

Reaction of 1a with Butanone. Formation of 3a. A solution of 1.02 g (3.26 mmol) of **1a** in 20 mL of butanone was stirred for 6 h, after which 30 mL of water was added. The solution was extracted with pentane and next with CH_2Cl_2. Evaporation of the pentane solution, dissolving in methanol, and precipitation with water gave 320 mg (1.50 mmol, 92%) of crude 10-methylphenothiazine. The CH_2Cl_2 solution was dried ($MgSO_4$), concentrated, and precipitated with ether, giving 375 mg (0.98 mmol, 60%) of crude **3a**. Crystallization from CH_2Cl_2–ether gave **3a**: mp 142–144 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 334 nm (4.6), 268 (5.2), 251 (6.4), 218 (20.0); ^1H NMR ($CDCl_3$) δ 7.94–7.16 (m, 8 H, aromatic), 5.47 (q, 1 H, –CH–, J = 7 Hz), 3.88 (s, 3 H, 10-CH_3), 2.26 (s, 3 H, CH_3CO-), 1.35 (d, 3 H, CH_3, J = 7 Hz).

Anal. Calcd for $C_{17}H_{18}NSClO_5$: C, 53.2; H, 4.73; N, 3.65; S, 8.34; Cl, 9.26. Found: C, 53.4; H, 4.88; N, 3.59; S, 8.21; Cl, 9.04.

Reaction of 1a with Methyl Isopropyl Ketone. Formation of 4. After stirring a solution of 978 mg (3.13 mmol) of **1a** in 20 mL of ketone for 90 min ether was added to precipitate 453 mg (1.14 mmol, 73%) of crude red-brown **4**. Decolorization and crystallization from CH_3CN gave colorless **4**: mp 116–119 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 340 nm (5.5), 320 (5.5), 272 (8.9), 219 (34.0); ^1H NMR (CD_3CN) δ 7.98–7.26 (m, 8 H, aromatic), 3.63 (s, 3 H, 10-CH_3), 2.14 (s, 3 H, CH_3CO-), 1.44 (s, 6 H, CH_3).

Anal. Calcd for $C_{18}H_{20}NSClO_5$: C, 54.4; H, 5.06; N, 3.52; S, 8.05; Cl, 8.93. Found: C, 54.3; H, 5.16; N, 3.58; S, 7.80; Cl, 8.80.

Workup of the filtrate from crude **4** gave 320 mg (1.50 mmol, 96%) of crude 10-methylphenothiazine.

Reaction of 1a with Acetophenone. Formation of 5. Use of 642 mg (2.05 mmol) of **1a** in 30 mL of ketone for 72 h and workup as with

4 gave 245 mg (0.57 mmol, 56%) of crude **5**. Crystallization from CH_3CN–ether gave **5**: mp 143–146 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 320 nm (6.8), 250 (23.4); ^1H NMR (Me_2SO-d_6) δ 8.18–7.34 (m, 13 H, aromatic), 5.42 (s, 2 H, $-CH_2-$), 3.73 (s, 3 H, 10-CH_3).

Anal. Calcd for $C_{21}H_{18}NSClO_5$: C, 58.4; H, 4.20; N, 3.24; S, 7.42; Cl, 8.23. Found: C, 58.5; H, 4.40; N, 3.50; S, 7.44; Cl, 8.45.

The mother liquor from crude **5** was worked up by TLC to give, with pentane, 228 mg (1.07 mmol, 104%) of crude 10-methylphenothiazine.

Reaction of 1a with Cyclopentanone. Formation of 6a. A solution of 967 mg (3.10 mmol) of **1a** and 1.5 mL of cyclopentanone in CH_3CN was stirred for 48 h, concentrated to small volume, and placed on a silica gel column. Elution with ether gave 10-methylphenothiazine which was purified by TLC to give 371 mg (1.71 mmol, 112%). Elution with acetone gave crude **6a**, which was decolorized and crystallized from CH_2Cl_2–ether, to give 250 mg (0.63 mmol, 20%) of **6a**: mp 112–113 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 324 nm (5.7), 271 (7.0), 253 (8.9), 222 (34); ^1H NMR (CD_3CN) δ 8.18–7.34 (m, 8 H, aromatic), 4.73 (t, 1 H, –CH–, J = 10 Hz), 3.74 (s, 3 H, 10-CH_3), 2.31 (m, 2 H, $-COCH_2$), 1.85 (m, 4 H, $-CH_2CH_2-$). Addition of D_2O caused the disappearance of the triplet at δ 4.73.

Anal. Calcd for $C_{18}H_{18}NSClO_5$: C, 54.6; H, 4.58; N, 3.53; S, 8.09; Cl, 8.95. Found: C, 54.8; H, 4.67; N, 3.71; S, 8.02; Cl, 8.71.

Reaction of 1a with Cyclohexanone. Formation of 7a. After reaction of 664 mg (2.13 mmol) of **1a** with 30 mL of cyclohexanone the ketone was pumped off and the residue worked up as for **6a**, giving 184 mg (0.864 mmol, 82%) of 10-methylphenothiazine and 230 mg (0.56 mmol, 52%) of **7a**: mp 117–118 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 328 nm (7.9), 271 (10.1), 253 sh, 220 (46.0); ^1H NMR ($CDCl_3$) δ 8.12–7.24 (m, 8 H, aromatic), 5.36 (d of d, J = 13 and 7 Hz), 3.90 (s, 3 H, 10-CH_3), 2.82–1.12 (m, 8 H, $-CH_2CH_2CH_2CH_2-$). The doublets at δ 5.36 disappeared on adding D_2O.

Anal. Calcd for $C_{19}H_{20}NSClO_5$: C, 55.7; H, 4.92; N, 3.42; S, 7.81; Cl, 8.65. Found: C, 55.9; H, 5.12; N, 3.48; S, 7.60; Cl, 8.57.

Reaction of 1a with Indanone. Formation of 9. A solution of 769 mg (2.46 mmol) of **1a** and 500 mg (3.78 mmol) of indanone-1 in 10 mL of CH_3CN was diluted after 7 h with 30 mL of water and extracted first with petroleum ether and next with CH_2Cl_2. Each extract was worked up as for **6a**, to give 270 mg (1.27 mmol, 103%) of 10-methylphenothiazine and 265 mg (0.60 mmol, 49%) of **9**: mp 110–112 °C; ^1H NMR (CD_3CN) δ 8.02–7.28 (m, 12 H, aromatic), 4.64 (2 d, 1 H, J = 7 and 4.5 Hz, –CH–), 3.72–3.14 (m, 5 H, 10-CH_3 and $-CH_2-$).

Reaction of 1a with Tetralone-1. Formation of 8a. A solution of 639 mg of **1a** in 5 mL of tetralone-1 was stirred for 2 h, during which time a precipitate formed. Ether was added to cause further precipitation, giving 420 mg (0.92 mmol, 90%) of crude, red-brown **8a**. This was decolorized in CH_3CN and recrystallized on adding ether, giving colorless **8a**: mp 141–142 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 335 nm (5.1), 304 (6.0), 252 (25.0); ^1H NMR (CD_3CN) δ 7.95–7.26 (m, 11 H, aromatic), 8.18 (d of d, 1 H, aromatic, J = 8 and 1.7 Hz), 5.01 (d of d, 1 H, α-CH, J = 14 and 5 Hz), 3.74 (s, 3 H, 10-CH_3), 3.00 (d of d, 2 H, γ-CH_2-, J = 7.5 and 3.5 Hz), 2.34–2.08 (m, 1 H, β-CH–), 1.66–1.42 (m, 1 H, β-CH–).

Anal. Calcd for $C_{23}H_{20}NSClO_5$: C, 60.4; H, 4.40; N, 3.06; S, 7.00; Cl, 7.74. Found: C, 60.5; H, 4.70; N, 3.36; S, 7.12; Cl, 7.97.

Reaction of 1b with Butanone. Formation of 3b. After stirring overnight a solution of 1.0 g (2.66 mmol) of **1b** in 20 mL of butanone the ketone was pumped off at room temperature, and the residue washed with 5 × 50 mL of petroleum ether. Decolorization and crystallization from CH_2Cl_2–ether gave 448 mg (1.0 mmol, 75%) of **3b**: mp 119–121 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 324 nm (7.58), 271 (5.91), 252 (10.8), 213 (35.3); ^1H NMR (acetone-d_6) δ 8.45–6.55 (m, 13 H, aromatic), 5.11 (q, 1 H, –CH–, J = 7 Hz), 2.25 (s, 3 H, $-CH_3$), 1.49 (d, 3 H, CH_3, J = 7 Hz).

Anal. Calcd for $C_{22}H_{20}NSClO_5$: C, 59.2; H, 4.52; N, 3.14; S, 7.19; Cl, 7.95. Found: C, 59.2; H, 4.57; N, 3.30; S, 7.39; Cl, 8.20.

The petroleum ether washings were concentrated and purified by TLC on silica gel plates (pentane) giving 375 mg (1.36 mmol, 102%) of 10-phenylphenothiazine.

Reaction of 1b with Cyclopentanone. Formation of 6b. Reaction of 410 mg (1.09 mmol) of **1b** and 10 ml of cyclopentanone for 4 h gave, as above, 160 mg (0.35 mmol, 64%) of **6b**: mp 111–112.5 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 323 nm (11.3), 272 (12.7), 253 (18.5).

Anal. Calcd for $C_{23}H_{20}SNClO_5$: C, 60.3; H, 4.40; N, 3.06; S, 7.00; Cl, 7.74. Found: C, 60.4; H, 4.37; N, 3.28; S, 6.77; Cl, 7.80.

TLC of the concentrated washings gave 165 mg (0.6 mmol, 110%) of 10-phenylphenothiazine.

Reaction of 1b with Cyclohexanone. Formation of 7b. Analogous reaction of 625 mg (1.66 mmol) of **1b** and 5 mL of cyclohexanone gave 250 mg (0.91 mmol, 110%) of 10-phenylphenothiazine and 162 mg (0.34 mmol, 41%) of **7b**: mp 121.5–122.5 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 326 nm (12.0), 273 (9.7), 254 (9.6).

Anal. Calcd for $C_{24}H_{22}SNClO_5$: C, 61.1; H, 4.70; N, 2.97; S, 6.79. Found: C, 60.9; H, 4.85; N, 3.19; S, 6.81.

Reaction of 1b with Tetralone-1. Formation of 8b. After stirring a solution of 375 mg (1.0 mmol) of **1b** in 5 mL of tetralone for 3 h, ether was added to precipitate **8b**. This was decolorized in CH_3CN and crystallized from CH_2Cl_2–ether to give 205 mg (0.39 mmol, 79%) of **8b**: mp 130–131 °C; λ_{max} (CH_3CN) (10^{-3} ϵ) 324 nm (10.1), 253 (27.0); ^1H NMR ($CDCl_3$) δ 8.19 (2 d, 1 H, aromatic), 8.07–7.23 (m, 14 H, aromatic), 6.82 (m, 2 H, aromatic), 4.98 (d of d, 1 H, –CH–, J = 14 and 5 Hz), 3.56–3.1 (m, 2 H, $-CH_2-$), 2.48–2.06 (m, 2 H, $-CH_2-$).

Anal. Calcd for $C_{28}H_{22}NSClO_5$: C, 64.7; H, 4.27; N, 2.69; S, 6.16; Cl, 6.82. Found: C, 64.5; H, 4.09; N, 2.87; S, 6.22; Cl, 7.03.

Filtrates were concentrated and purified by TLC (silica gel, pentane) giving 124 mg (0.45 mmol, 90%) of 10-phenylphenothiazine.

Formation of Ylides 10–13b. A small amount (0.3–1.5 mmol) of the sulfonium salts **3b, 6b–8b** was dissolved in 20 mL of methanol and 1 mL of triethylamine was added. After 1 min 250 mL of water was added and the solution was extracted with 3 × 50 mL of CH_2Cl_2. After drying over K_2CO_3 the solvent was pumped off and the residue crystallized and characterized by mass and NMR spectroscopy. Ylide **10**, 96% yield, had mp 123–125 °C (from CH_2Cl_2–ether–petroleum ether); *m/e* 345.1174 (calcd, 345.1176); ^1H NMR (CD_3CN) δ 8.00–7.03 (m, 11 H, aromatic), 6.53–6.26 (m, 2 H, aromatic), 2.33 (s, 3 H, $-CH_3$), 1.43 (s, 3 H, $-CH_3$). Ylide **11**, 82% yield, had mp 159.5–161 °C (from CH_2Cl_2–ether–petroleum ether); *m/e* 357.1162 (calcd, 357.1176); and ^1H NMR ($CDCl_3$) δ 7.92–6.42 (m, 13 H, aromatic), 2.4–1.4 (m, 6 H, C_5 ring). Ylide **12**, 88% yield, had mp 119–120 °C (from CH_2Cl_2–ether–petroleum ether); *m/e* 371.1290 (calcd, 371.1333); and ^1H NMR ($CDCl_3$) δ 7.85–7.0 (m, 11 H, aromatic), 6.55–6.35 (m, 2 H, aromatic), 2.38–1.4 (m, 8 H, C_6 ring). Ylide **13b**, 93% yield, had mp 115–117.5 °C (from CH_2Cl_2–ether–petroleum ether); *m/e* 419.133 (calcd, 419.133); ^1H NMR ($CDCl_3$) δ 8.36–6.20 (m, 17 H, aromatic), 3.1–2.1 (m, 4 H, $-CH_2CH_2-$).

Formation of Ylide 13a. Treatment of 694 mg (1.51 mmol) of **8a** in 15 mL of CH_3CN with 0.5 mL of *tert*-butylamine for 10 min gave 467 mg of white precipitate. This was suspended in water and extracted with CH_2Cl_2 giving 435 mg (1.22 mmol, 81%) of **13a**: mp 130–131 °C (from CH_2Cl_2–ether); ^1H NMR ($CDCl_3$) δ 8.06 (m, 1 H, aromatic), 7.64–6.98 (m, 11 H, aromatic), 3.46 (s, 3 H, 10-CH_3), 2.72 (t, 2 H, $-CH_2-$, J = 7.5 Hz), 2.09 (t, 2 H, $-CH_2-$, J = 7.5 Hz).

Anal. Calcd for $C_{23}H_{19}NSO$: C, 77.3; H, 5.36; N, 3.92. Found: C, 77.2; H, 5.42; N, 4.01.

Reaction of 9 with Nucleophiles. Formation of α-Substituted Indanones (14–18). Reactions were carried out by stirring a solution of **9** in 10 mL of CH_3CN with the nucleophile for several hours. Workup then varied among the cases. The mixture from ammonium bromide (500 mg, 5.1 mmol) and **9** (294 mg, 0.66 mmol) was diluted with water and extracted with CH_2Cl_2, and the CH_2Cl_2 solution was dried, concentrated, and streaked on silica gel plates. Development with ether–pentane (90:10) gave 88 mg (0.41 mmol, 62%) of 10-methylphenothiazine and 91 mg (0.43 mmol, 65%) of 2-bromo-1-indanone (**17**), mp 33–34 °C (from ethanol) (lit. mp 37–38.5 °C),[13] *m/e* 211.97 (calcd, 211.97). The mixture from 500 mg (6.2 mmol) of sodium thiocyanate and 140 mg (0.32 mmol) of **9** was concentrated and streaked on TLC plates as above, giving 62 mg (0.29 mmol, 92%) of 10-methylphenothiazine and 45 mg (0.24 mmol, 76%) of **14**, mp 92–93 °C (from ether-pentane); λ_{max} (CH_3CN) (10^{-3} ϵ) 290 nm (1.3), 246 (14.0) (lit. mp 91–92 °C[14]).

The mixture from 800 mg (4.04 mmol) of sodium *p*-toluenesulfinate·$2H_2O$ and 312 mg (0.663 mmol) of **9** was concentrated and placed on a silica gel column. Elution with ether–pentane (10:90) gave 104 mg (0.49 mmol, 70%) of 10-methylphenothiazine; elution with CH_2Cl_2 gave 102 mg (0.32 mmol, 46%) of **15**, mp 141–142 °C (from ethanol), λ_{max} (CH_3CN) (10^{-3} ϵ) 290 nm (1.6), 246 (10.1); *m/e* 286.07 (calcd, 286.07). The mixture from 300 mg (1.87 mmol) of potassium ethylxanthate and 607 mg (1.37 mmol) of **9** was worked up similarly to give 255 mg (1.20 mmol, 88%) of 10-methylphenothiazine and 276 mg (1.10 mmol, 80%) of **16**, mp 77–78 °C (from ethanol), λ_{max} (CH_3CN) (10^{-3} ϵ) 280 nm (15.1), 242 nm (16.4).

Anal. Calcd for $C_{12}H_{12}S_2O_2$ (16): C, 57.1; H, 4.79; S, 25.4. Found: C, 57.0; H, 4.75; S, 25.8.

The mixture from 1 mL (12.4 mmol) of pyridine and 631 mg (1.42 mmol) of **9** was concentrated and diluted with ethyl acetate. A light brown precipitate (183 mg) was suspended in water and extracted with CH_2Cl_2. The CH_2Cl_2 solution gave 48 mg (0.155 mmol, 11%) of 2-pyridinium-1-indanone perchlorate (**18**), mp 218–219 °C (from CH_2Cl_2–ether).

Anal. Calcd for $C_{14}H_{12}NClO_5$ (18): C, 54.3; H, 3.90; Cl, 11.5. Found:

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C, 54.2; H, 3.88; Cl, 11.6.

Registry No.—**1a**, 54014-67-4; **1b**, 52156-15-7; **2**, 61723-13-5; **3a**, 62723-15-7; **3b**, 61723-17-9; **4**, 61723-19-1; **5**, 61723-21-5; **6a**, 61723-23-7; **6b**, 61723-25-9; **7a**, 61723-27-1; **7b**, 61723-29-3; **8a**, 61723-31-7; **8b**, 61723-33-9; **10**, 61723-34-0; **11**, 61723-35-1; **12**, 61723-36-2; **13a**, 61723-37-3; **13b**, 61723-38-4; acetone, 67-64-1; butanone, 78-93-3; methyl isopropyl ketone, 563-80-4; acetophenone, 98-86-2; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; indanone-1, 83-33-0; tetralone-1, 529-34-0; sodium thiocyanate, 540-72-7; sodium *p*-toluenesulfinate, 824-79-3; potassium ethylxanthate, 140-89-6; pyridine, 110-86-1.

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(2) Supported by the National Science Foundation, Grant MPS 75-02794.
(3) Work with 10-methylphenothiazine cation radical in partial fulfillment of requirements of the M.S. degree of A.G.P.
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Reaction of Electrogenerated Nitrobenzene Radical Anion with Alkyl Halides

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Nitrobenzene radical anion formed by the electrochemical reduction of nitrobenzene reacts rapidly with alkyl halides. Electrochemical reduction of nitrobenzene in the presence of alkyl halides leads to a high yield of *N,O*-dialkylphenylhydroxylamines.

The electrochemical reduction of nitrobenzene in aprotic solvents has been studied in detail during the past two decades.[1,2] Nitrobenzene is reduced in two steps, first to a radical anion (eq 1) and then at more negative electrode potentials directly to a dianion (eq 2). Both steps are reversible, but generally the dianion reacts rapidly with solvent, electrolyte, or trace impurities so that the dianion may be observed only under rigorously controlled conditions.[3] The radical anion of nitrobenzene, however, is much less reactive. It has been detected even in strongly basic aqueous solution by ESR spectroscopy.[4,5] The reaction of nitrobenzene radical anion with various proton donors has been studied in detail[1-3] and, generally, if a proton donor is present during nitrobenzene reduction, then phenylhydroxylamine is formed (eq 3). The electrogenerated nitrobenzene radical anion is generally considered to be quite stable and, therefore, reactions other than with proton donors have been studied very little.

$$C_6H_5NO_2 \overset{1e}{\rightleftharpoons} C_6H_5NO_2^{-}\cdot \qquad (1)$$

$$C_6H_5NO_2 \overset{2e}{\rightleftharpoons} C_6H_5NO_2^{2-} \qquad (2)$$

$$C_6H_5\text{-}NO_2 \xrightarrow[4e^-]{4H^+} C_6H_5\text{-}NHOH + H_2O \qquad (3)$$

This paper deals with the reduction of nitrobenzene in dimethylformamide in the presence of simple alkyl halides, which have been found to react rapidly with nitrobenzene radical anion leading in several steps to substituted phenylhydroxylamines. A similar product was obtained when nitrobenzene was reduced in the presence of acetic anhydride, producing *N,O*-diacetylphenylhydroxylamine.[6] Alkyl halides recently have been found to react with many types of electrogenerated anions and radical anions, such as those formed by reduction of ketones and imines,[7] activated olefins,[8-10] Schiff bases,[11] and disulfides.[12]

Results and Discussion

The stability of nitrobenzene radical anion is demonstrated by cyclic voltammetry (Figure 1) carried out at a hanging mercury drop electrode in dimethylformamide (DMF) containing 0.1 M tetraethylammonium perchlorate (TEAP). The presence of an anodic peak, on reversing the direction of voltage sweep just after the initial reduction peak of nitrobenzene, indicates that the nitrobenzene radical anion is not being rapidly consumed in a follow-up chemical reaction. As shown in Figure 1, addition of 1-bromobutane to the solution causes the anodic peak to decrease in size, indicating that the radical anion is reacting with butyl bromide.

Although it is possible to determine the rate of the reaction of nitrobenzene radical anion with 1-bromobutane by cyclic voltammetry or cyclic chronopotentiometry, the theoretical treatment of this set of reactions (eq 12–16) is complex. A sense of the relative rates of reaction of nitrobenzene radical anion with 1-bromobutane and 1-iodobutane may be gained from cyclic chronopotentiometry (Figure 2). In the absence of a follow-up reaction the reverse transition time is one-third of the forward electrolysis time.[13] Reactions consuming the radical anion cause the reverse transition time to be shorter. For a solution of 1.3 mM nitrobenzene, the decrease in the reverse transition time is about the same when 0.5 M 1-bromobutane is present as it is when 0.05 M 1-iodobutane is present. In other words, it requires ten times as much 1-bromobutane as 1-iodobutane to obtain the same apparent rate of disappearance of nitrobenzene radical anion.

The preparative electrochemical reduction of nitrobenzene at −1.3 V vs. SCE (the potential at which nitrobenzene radical anion is formed) in the presence of 1-chlorobutane, 1-bro-

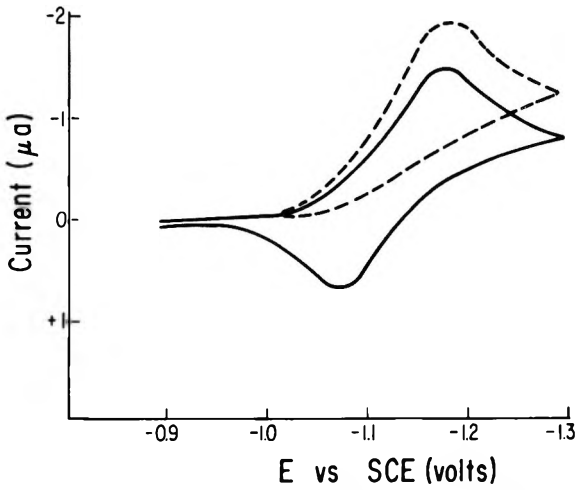


Figure 1. Cyclic voltammograms of nitrobenzene (1.275 mM) in DMF containing 0.1 M TEAP at a hanging Hg drop electrode in the absence (solid line) and presence (dashed line) of butyl bromide (0.3 M). Scan rate 50 mV/s.

mobutane, or 1-iodobutane produces in each case a good yield of *N,O*-dibutylphenylhydroxylamine (eq 4). Chloromethane

$$C_6H_5NO_2 + 2BuX \longrightarrow C_6H_5N(Bu)OBu \quad (4)$$

or methyl-*p*-toluenesulfonate each react to form *N,O*-dimethylphenylhydroxylamine. The dihaloalkane (1,5-dibromopentane) reacts to form a cyclic compound, *N*-phenylperhydro-1,2-oxazepine (eq 5). All of these reactions required 4 Faradays of electricity per mol of nitrobenzene present.

$$C_6H_5NO_2 + Br(CH_2)_5Br \xrightarrow{\text{reduction}} C_6H_5{-}N\langle \quad (5)$$

These reactions are examples of a simple method for synthesis of a large variety of trisubstituted hydroxylamines. A few trisubstituted phenylhydroxylamines have been prepared[14] before, but the synthetic utility of previous methods is limited.

The reaction scheme proposed for the formation of the substituted phenylhydroxylamines follows:

$$C_6H_5NO_2 \xrightarrow{1e^-} C_6H_5NO_2^{-\cdot} \quad (6)$$

$$C_6H_5NO_2^{-\cdot} + RX \xrightarrow[\text{slow}]{} C_6H_5{-}\overset{\overset{O}{|}}{\underset{\cdot}{N}}{-}O{-}R + X^- \quad (7)$$

$$C_6H_5{-}\overset{\overset{O}{|}}{\underset{\cdot}{N}}{-}OR \xrightarrow{1e} C_6H_5{-}N{=}O + OR^- \quad (8)$$

$$OR^- + RX \longrightarrow ROR + X^- \quad (9)$$

$$C_6H_5NO + 2\,RX \xrightarrow{2e^-} C_6H_5{-}\underset{\underset{R}{|}}{N}OR + 2X^- \quad (10)$$

Equation 7 is thought to be the slow step, because cyclic voltammetry and cyclic chronopotentiometry of nitrosobenzene showed that the rate of reaction of nitrosobenzene radical anion with 1-bromobutane was much faster than that of nitrobenzene radical anion with 1-bromobutane. Values for the rate constant were not determined for the reaction of nitrosobenzene radical anion with 1-bromobutane because other reactions, such as dimerization or reaction with unreduced nitrosobenzene,[15,16] were consuming nitrosobenzene radical anion.

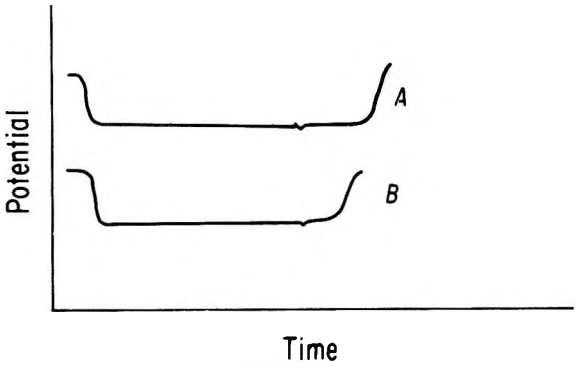
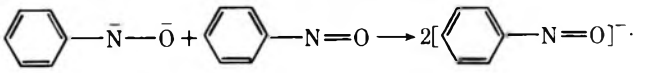


Figure 2. Cyclic chronopotentiogram of 1.36 mM nitrobenzene in DMF containing 0.1 M TEAP at a hanging Hg drop electrode in the absence (A) and presence (B) of butyl bromide (0.54 M).

Dibutyl ether was present in the electrolysis product of the reduction of nitrobenzene in the presence of 1-bromobutane (eq 9).

Equation 10 is shown as a single step because an electrolysis of nitrosobenzene in the presence of 1-bromobutane at −0.9 V vs. SCE did not produce *N,O*-dibutylphenylhydroxylamine, while reduction at −1.5 V vs. SCE did produce *N,O*-dibutylphenylhydroxylamine. At −1.5 V vs. SCE nitrosobenzene is converted directly to the dianion[16] which would be expected to react rapidly with 1-bromobutane. Even at −1.5 V vs. SCE, the yield of *N,O*-dibutylphenylhydroxylamine was not as high as was obtained from nitrobenzene, presumably because of the disproportionation reaction (eq 11). Dimerization of the



(11)

nitrosobenzene radical anion or coupling of nitrosobenzene and its radical anion are presumably the competing reactions which lower the yield of the substituted hydroxylamine at −1.5 V vs. SCE and effectively inhibit the reaction when the reduction is carried out at −0.9 V vs. SCE.

An attempt to carry out a similar reaction using nitrocyclohexane rather than nitrobenzene in the presence of 1-bromobutane led to cyclohexanone oxime rather than the expected *N,O*-dibutyl-N-cyclohexylhydroxylamine. A similar electrolysis of nitrocyclohexane in the absence of 1-bromobutane gave only traces of cyclohexanone oxime. Those results may be rationalized by the following reaction scheme:

$$C_6H_{11}NO_2 \xrightarrow{1e} C_6H_{11}NO_2^{-\cdot} \quad (12)$$

$$C_6H_{11}NO_2^{-\cdot} + BuBr \longrightarrow C_6H_{11}{-}\underset{\underset{O}{|}}{N}{-}OBu \quad (13)$$

$$C_6H_{11}{-}\overset{\overset{O}{|}}{\underset{\cdot}{N}}{-}OBu \xrightarrow{1e} C_6H_{11}{-}\overset{\overset{O}{|}}{\underset{-}{N}}{-}OBu \quad (14)$$

$$C_6H_{11}{-}\overset{\overset{O}{|}}{\underset{-}{N}}{-}OBu \xrightarrow[\text{in bulk}]{\text{slow}} C_6H_{11}NO + BuO^- \quad (15)$$

$$C_6H_{11}NO \xrightarrow[\text{base}]{\text{rapid}} \text{(cyclohexanone oxime)} \quad (16)$$

The scheme is similar to that proposed for nitrobenzene, except that nitrosocyclohexane is rapidly converted by base (eq 16) to the oxime which is not reducible at the potential of the reaction. In the absence of an electrophile to react rapidly with the nitrocyclohexane radical anion, the most likely reaction is cleavage of the C–N bond[17] to form nitrite ion and cyclohexyl radical.

Experimental Section

Cyclic voltammetry and cyclic chronopotentiometry were carried out at a hanging Hg drop using a Princeton Applied Research Model 173 potentiostat driven by a Princeton Applied Research Model 175 universal programmer. The cell used for electroanalytical experiments had a working volume of 50 mL. It contained the hanging mercury drop working electrode, Pt wire secondary electrode, and SCE reference which was isolated from the electrolyte by a fine glass frit. The solution was deaerated with N_2 before analysis.

NMR spectra were obtained with a Varian T-60 NMR spectrometer. Mass spectra were obtained on a Varian MAT CH7A mass spectrometer. Gas chromatographic analyses were performed using a 6 ft × 0.125 in. column packed with 5% OV-17 on 80–100 mesh Chromosorb W.

General Electrolysis Procedure. The electrolyses were carried out in a coarse glass frit divided H cell with a 7-cm diameter Hg pool cathode and 1 $in.^2$ Pt foil anode. The cathode compartment contained 300 mL of DMF with 0.2 M electrolyte, 0.05 mol of nitro compound, and 0.2 mol of alkyl halide or tosylate. The cathode potential was monitored by a saturated calomel electrode separated from the bulk catholyte by a porous ceramic plug. All electrolyses were carried out under N_2 at a constant cathode potential using a Wenking Model PCA 72H Potential Control Amplifier. The total electricity passed during the electrolysis was measured by passing the current through a dc motor coupled to an odometer.

The dimethylformamide used as a solvent was dried over Linde 3A molecular sieves. The electrolyte was 0.2 M tetrabutylammonium bromide or iodide or tetraethylammonium *p*-toluenesulfonate or chloride predried in a vacuum desiccator. The choice of anion was dictated by the alkyl halide or tosylate used.

The electrolyses were generally carried to completion as indicated by the current being less than 10% of the initial current. The catholyte was then diluted with twice its volume of benzene and extracted three times with water. The benzene solution was dried over anhydrous $MgSO_4$ and then the benzene was removed on a rotary evaporator to give the crude product. When tetrabutylammonium iodide was used, the crude product was extracted with ether to separate the products from the electrolyte.

Reduction of Nitrobenzene in the Presence of 1-Bromobutane. The electrolysis was run at −1.3 V vs. SCE with the initial current being 150 mA. After 47 h, 0.185 Faraday of electricity had been passed (3.7 Faraday/mol nitrobenzene). Ten grams (90%) of crude product was obtained. The crude *N,O*-dibutylphenylhydroxylamine was distilled at reduced pressure (0.05 mm), the major portion distilling at 80 °C accompanied by some decomposition. Redistillation of a portion gave a colorless liquid, bp 65 °C (0.025 mm), n^{22}_D 1.4920. Another portion of the first distillate was purified by chromatography on silica gel eluting with 50/50 benzene/hexane. Evaporation of the solvent gave an oil which by GC analysis was identical with the redistilled material. Both samples gave satisfactory elemental analyses. ^{1}H NMR ($CDCl_3$) δ 0.97 (6 H, t, CH_3), 1.53 (8 H, m, CH_2), 3.26 (2 H, t, J = 7 Hz, CH_2N), 3.78 (2 H, t, J = 6.5 Hz, CH_2O), 7.18 (5 H, m, aromatic).

Reduction of Nitrobenzene in the Presence of 1-Iodobutane. The electrolysis was carried out at −1.3 V vs. SCE for 64 h, and a total of 0.24 Faraday passed (4.8 Faradays/mol nitrobenzene). The crude product (10.2 g) was 90% *N,O*-dibutylphenylhydroxylamine (83%) by GC analysis.

Reduction of Nitrobenzene in the Presence of 1-Chlorobutane. The electrolysis was carried out at −1.35 V vs. SCE for 40 h, and a total of 0.19 Faraday had passed (3.8 Faradays/mol nitrobenzene). The crude product contained 7.6 g (69%) of *N,O*-dibutylphenylhydroxylamine by GC analysis.

Reduction of Nitrosobenzene in the Presence of 1-Bromobutane. The catholyte contained 5.35 g of nitrosobenzene and 15 g of 1-bromobutane. The electrolysis was carried out at −1.1 V vs. SCE for 20 h, and 0.03 Faraday of electricity was passed (0.6 Faraday/mol nitrosobenzene). The crude product (5.4 g) contained no *N,O*-dibutylphenylhydroxylamine by GC analysis.

A second electrolysis, as above except carried out at −1.5 V vs. SCE, was operated for 20 h, and 0.084 Faraday of electricity passed (1.68 Faradays/mol of nitrosobenzene). The crude product contained 3 g (27% yield) of *N,O*-dibutylphenylhydroxylamine by GC analysis.

Reduction of Nitrobenzene in the Presence of Chloromethane. The catholyte consisted of 300 mL of DMF containing 0.2 M $Et_4N^+Cl^-$, 6.15 g of nitrobenzene, and saturated with chloromethane. Chloromethane was bubbled through the catholyte continuously during the electrolysis. The electrolysis was run at −1.3 V vs. SCE for 40 h, and a total of 0.193 Faraday of electricity was passed (3.86 Faradays/mol nitrobenzene). The crude product (6.2 g) was estimated to be 85% *N,O*-dimethylphenylhydroxylamine by GC (80% yield). Distillation of the crude product gave pure *N,O*-dimethylphenylhydroxylamine: bp 67–68 °C (10 mm); n^{22}_D 1.5170; ^{1}H NMR ($DCCl_3$) δ 3.00 (3 H, s, CH_3N), 3.63 (3 H, s, CH_3O), 7.03 (5 H, m, aromatic).

Reduction of Nitrobenzene in the Presence of Methyl *p*-Toluenesulfonate. The electrolysis was run at −1.3 V vs. SCE for 42 h, and 0.19 Faraday was passed (3.8 Faradays/mol of nitrobenzene). Analysis of the crude product by GC indicated the presence of 2.5 g (36% yield) of *N,O*-dimethylphenylhydroxylamine along with considerable amounts of unidentified material.

Reduction of Nitrobenzene in the Presence of 1,5-Dibromopentane. The electrolysis was run at −1.3 V vs. SCE for 44 h, and a total of 0.19 Faraday passed (3.8 Faradays/mol nitrobenzene). The crude product (11.5 g) was distilled, the major component boiling at 71–77 °C (0.025 mm) with some decomposition. Further purification by chromatography on silica gel eluting with 80/20 hexane/benzene gave, after solvent evaporation, an oil which contained only one component by GC analysis. The mass spectral data and NMR were consistent with *N*-phenylperhydro-1,2-oxazepine: ^{1}H NMR ($DCCl_3$) δ 1.82 (6 H, m, CH_2), 3.33 (2 H, m, CH_2N), 3.97 (2 H, m, CH_2O), 7.02 (5 H, m, aromatic); mass spectrum M^+·m/e (rel intensity) 177 (42), 159 (100), 158 (63), 130 (39), 122 (31), 106 (30), 105 (44), 104 (39).

Reduction of Nitrocyclohexane in the Presence of 1-Bromobutane. The electrolysis was run at −1.8 V vs. SCE for 20 h, and a total of 0.053 Faraday was passed (1 Faraday/mol nitrocyclohexane). GC analysis of the crude product indicated that it contained 3 g of cyclohexanone oxime. Distillation gave pure cyclohexanone oxime, bp 208 °C, identical with an authentic sample.

Acknowledgment. This paper was presented in part at the Electrochemical Society, Inc., meeting in Philadelphia, Pa., May 1977.

Registry No.—Nitrobenzene, 98-95-3; 1-bromobutane, 109-65-9; *N,O*-dibutylphenylhydroxylamine, 61915-46-6; 1-iodobutane, 542-69-8; 1-chlorobutane, 109-69-3; nitrosobenzene, 586-96-9; chloromethane, 74-87-3; *N,O*-dimethylphenylhydoxylamine, 61915-47-7; methyl *p*-toluenesulfonate, 80-48-8; *N*-phenylperhydro-1,2-oxazepine, 61915-48-8; 1,5-dibromopentane, 111-24-0; nitrocyclohexane, 1122-60-7; nitrobenzene radical anion, 12169-65-2.

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Broad Spectrum Methods for the Resolution of Optical Isomers. A Discussion of the Reasons Underlying the Chromatographic Separability of Some Diastereomeric Carbamates

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Diastereomeric pairs of carbamates (**4a, b–26a, b**) were synthesized and separated chromatographically on a preparative scale. These carbamate diastereomers display a correlation between structure, stereochemistry, and elution order. In addition, consistent NMR spectral differences observed between pairs of diastereomers correlate with established stereochemistry. These spectral correlations, $Eu(fod)_3$ gradients, and "acylation shifts" indicate that the carbamate diastereomers uniformly show a preference for solution conformations **2a** and **2b**. The population of these conformations in solution appears related to the origin of the chromatographic separability of the diastereomers and a rationale for this relationship is presented. All of the diastereomeric carbamates so investigated show evidence of a dynamic equilibrium between the *E* and *Z* (*Z*:*E* ≃ 90:10) rotamers at 220 MHz and 27 °C in the presence of $Eu(fod)_3$. The possible effect of such an equilibrium on the chromatographic separability of these diastereomers is discussed.

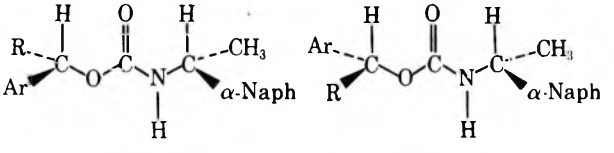
We recently reported[1] the resolution of 2,2,2-trifluoro-1-(1-naphthyl)ethanol, a useful chiral solvating agent, via the automated multigram chromatographic separation[2] of diastereomeric carbamate derivatives. In this paper, we address ourselves to the reasons underlying the chromatographic separability of this and other structurally similar carbamate diastereomers.

On the basis of our own work and the pioneering efforts of others, we feel that most "first time" resolutions of enantiomers will soon be effected almost solely by liquid chromatographic techniques. Historically, the usual approach to resolution has involved an empirical search for a chiral derivatizing agent (CDA) that will convert the racemate into a mixture of diastereomers separable by fractional crystallization.[3] This approach can be time consuming, inefficient in overall yield, and may provide but one enantiomer in appreciable (but possibly uncertain) optical purity. In contrast, the chromatographic behavior of many diastereomers will follow systematic rules that, once understood, will allow rational selection of CDA that afford predictable separations of the diastereomers. The widely held view that liquid chromatography is a cumbersome method for effecting preparative scale separations is obsolete; our recent reports[1,2] give a clear portent as to the future of large scale chromatographically effected resolutions. Apart from their potential predictability, chromatographic resolutions will generally afford both enantiomers in high yield and high optical purities. Finally, CDA of known absolute configuration potentially provide information concerning the absolute configurations of the derivatized solutes through differences in the spectral and chromatographic properties of the diastereomeric derivatives.

Results and Discussion

Chromatographic Behavior. The diastereomers derived from reaction of alkylarylcarbinols with chiral 1-(1-naphthyl)ethyl isocyanate[4] (**1**) are generally separable on a preparative scale by chromatography on alumina with benzene (Table I). In the present instances, we observe a correlation between structure, stereochemistry, and elution order of these diastereomers. The stereochemistry of the diastereomers entered in Table I has been determined by hydrolysis of the separated diastereomers and determination[5] of the absolute configuration of the liberated alcohols. We also note consistent NMR spectral differences between diastereomers that correlate with stereochemistry and thereby suggest uniform conformational behavior for these carbamates.

A recent NMR study[6] of esterlike derivatives of secondary alcohols similar to those presently employed discusses the use of "acylation shifts" and $Eu(fod)_3$ gradients to support carbinyl hydrogen bonding (CHB) as an effective agent for conformational control. As a consequence of CHB, the carbamate conformations (or their weighted time-averaged equivalents) depicted in **2a** and **2b** are thought to be substantially populated in nonpolar solvents. These conformations account for the consistent chemical shift differences observed (Table I) between the methyl doublets of diastereomeric pairs **4a,b–21a,b**, as well as the correlation of the sense of this chemical shift difference with known stereochemistry. Owing to the shielding effect of the cis aryl group, the methyl doublet resonance of **2b** occurs upfield to that of **2a**. To avoid continual recourse to stereochemical convention, these carbamate diastereomers are designated as "erythroid", **2a**, and "threoid", **2b**. These depicted conformations also represent a useful



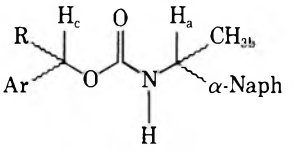
2a erythroid 2b threoid

initial vantage point for consideration of the observed correlations between structure, stereochemistry, and elution order as well as the NMR–stereochemical correlation. Although a more detailed conformational discussion is subsequently presented, we presently point out that the natures of the alkyl and aryl substituents appear to play but secondary roles in determining "backbone" conformational preferences for the diastereomers in Table I.

Mechanisms of Chromatographic Separation. There are two limiting general mechanisms for separation by adsorption chromatography. At one extreme, separability derives entirely from differential solvation of the solutes by the elution solvent. At the other,[7] separability stems solely from differential probabilities for or energies of adsorption for solutes and is independent of the solvent. A blend of both processes is operative in the separation of diastereomers.[8] Helmchen,[9] among others,[10] has used the concept of differential ease of approach to the adsorbent in rationalizing the separation of certain kinds of diastereomers by liquid chromatography. This rationale is closely related to that used earlier by Karger and co-workers[8,11a–c] to explain the gas chromatographic separability of diastereomeric esters and amides.

Helmchen's rationale, pertinent to our results, stems from

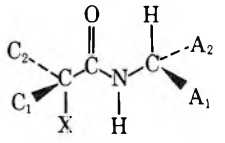
Table I. NMR and Chromatographic Properties of Some Carbamate Diastereomers



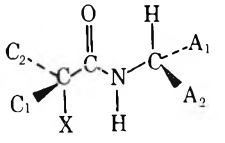
Compd	R	Ar	Chemical shift data[d] δa	δb	Δδa[e]	Δδb[e]	δc	Δδc[e]	Chromatographic data K1′	K2′	α	Mp,[i] °C High Rf	Low Rf
4	CF_3	C_6H_5	5.54	1.48	0.01	0.05	6.04	0.00	3.3	5.2	1.58	130–131	120–121
5	CF_3	p-$CH_3C_6H_4$	5.62	1.54	0.02	0.04	6.06	0.00	2.9	4.4	1.52	137–139	133–133.5
6	CF_3	p-FC_6H_4	5.61	1.62	−0.03	0.04	6.18	0.02	2.4	4.9	2.04	131–133	130–131
7	CF_3	m-NO_2-C_6H_4	5.67	1.61	−0.05	0.07	6.26	0.00			1.58	137–139	
8	CF_3	α-Naph	5.58	1.46	0.02	0.08	7.02	0.01	3.0	4.7	1.56	139–140	123
9	CF_3	3-Pyrenyl	5.67	1.60	0.03	0.12	>7.00[g]		3.2	5.4	1.64	186–188	190
10	CF_3	9-Anthryl	5.50	1.56	−0.10	−0.36	>7.00[g]		3.8	5.3	1.40		
11	CF_3	10-CH_3-9-anthryl	5.42	1.55	0.03	−0.42	>7.00[g]		2.4	3.2	1.33	115–118	110
12	C_3F_7	C_6H_5	5.60	1.54	0.03	0.14	6.26	0.02	1.7	3.6	2.12	141–143	122–122.5
13	C_3F_7	α-Naph	5.57	1.44	0.04	0.14	>7.00[g]		1.7	3.6	2.12	*j*	*j*
14	C_3F_7	9-Anthryl	5.40	1.29	0.00	0.20	>7.00[g]				1.00	*j*	*j*
15	CBr_3	C_6H_5	5.62	1.62	0.00	0.07	6.27	0.01	6.0	9.3	1.55	*j*	*j*
16	CH_3	C_6H_5	5.55	1.44	−0.05	−0.08	5.71	0.00	15.0	19.5	1.30	*j*	*j*
17	CH_3	α-Naph[f]	5.67	1.62	0.01	−0.06	*f*	*f*			1.20	*j*	*j*
18	C_2H_5	α-Naph	5.64	1.58	0.00	0.08	6.44	0.00			1.25	*j*	*j*
19	C_2H_5	C_6H_5	5.37	1.50	0.02	0.08	5.57	0.02			1.22[h]	*j*	*j*
20	$C(CH_3)_3$	α-Naph	5.65	1.52	−0.11	0.08	6.45	−0.05	18.0	23.5	1.31	*j*	*j*
21	$C(CH_3)_3$	C_6H_5	5.48	1.46	−0.04	0.14	5.44	−0.08	25.2	33.7	1.30	*j*	*j*

[d] Chemical shifts (δ) are given for the *low* R_f diastereomer in parts per million, downfield of Me_4Si. [e] $\Delta\delta = \delta_{high\ R_f} - \delta_{low\ R_f}$. [f] Data for *l*-*d* substituted diastereomer. [g] Buried in the aromatic region. [h] This carbamate was chromatographed on silica gel with CH_2Cl_2–hexane (7:3). [i] All of the carbamates in this table gave satisfactory mass spectra or elemental analyses or both. [j] Not determined.

the observation that the diastereomers of certain amides appear to preferentially populate conformations **3a** and **3b** in



3a



3b

solution. The diastereomers having the smallest A and the smallest C substituents on the same conformational face are found to be chromatographically the least mobile, and Helmchen suggests that steric hindrance of approach to the adsorbent determines elution order. Feibush[12] has expressed this same concept in terms of "bulkiness chirality".

Despite the success of the steric "ease of approach" type model, it is conceptually bothersome to suppose that the conformational behavior in solution of conformationally mobile molecules will exert control over chromatographic behavior. If two diastereomers are chromatographically separable, it is because their energies of adsorption are nonidentical. Conformation *while adsorbed* is surely relevant to adsorption energy. However, little is known about conformations of adsorbed molecules and they may be unlike those populated in solution. In general, the energy provided by adsorption of a moderately polar molecule upon silica gel or alumina should be great enough to disrupt most *solution* conformations should they be unfavorable *adsorption* conformations. If adsorption does cause conformational change, then the possibility arises that adsorption energies for separable diastereomers may differ, at least in part, because the energies required to disrupt the solution conformations of the diastereomers are different. Thus, diastereomers having stereochemically dependent intramolecular interactions should generally be separable by chromatography. For example, erythro and threo diol diastereomers differ in their degrees of intramolecular hydrogen bonding and hence also in their chromatographic behavior.[8] However, in Helmchen's amides,[15] in Karger's esters and amides, and in our carbamates, there is no reason to suspect the existence of significant differences in conformational "disruption energies" between diastereomers. Nevertheless, the diastereomers are chromatographically separable and the separations improve with a restriction of conformational mobility.[16] From the correlation noted between the solution conformations of a series of diastereomeric carbamates, structure, and stereochemistry, we infer that carbamate conformations *while adsorbed* are rather similar to those noted in solution. This surprising inference cannot be directly substantiated, yet it is consistent with a body of data.

In the case of the presently discussed carbamates, the principal adsorption site(s) presumably lies between the chiral centers. Hence, the most important aspects of conformational control are those that govern the spatial relationship of one chiral assembly with respect to the other. In carbamate conformations **2a** and **2b**, conformational control and rigidity is provided by carbinyl hydrogen bonding (CHB).[6] Superimposed upon this "backbone" effect will be conformational preferences of backbone substituents (i.e., the alkyl and aryl groups) and possible interactions between these substituents and the adsorbent.

Assuming the preferential population of conformations similar to **2a** and **2b**, it is clear from the elution orders in Table I that the Karger–Helmchen steric ease of approach model is only partially successful. For example, for methyl bearing carbamates **16** and **17**, the elution order is that expected on the basis of this model, in that the threoid isomers are the first to be eluted. For these diastereomers the erythroid isomer bears both "small" groups (i.e., the methyls) on the same face of the backbone and is expected to be most strongly adsorbed.

Unexpectedly, the elution order of the diastereomers *inverts* when R is *ethyl, propyl, trifluoromethyl,* etc. In terms of van der Waals radii, these groups are smaller than phenyl or other aryl substituents and no inversion of steric order has occurred.

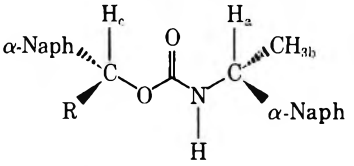
A serious omission of the steric model is that it neglects other possible modes of interaction between substituents and adsorbent. Even a partial understanding of the chromatographic behavior of diastereomers requires not only conformational knowledge but also an appreciation of the "effectiveness scale" for the ability of substituents to ward off (or bind to) the stationary phase. In the case of a homologous series of alkyl groups, "warding off" ability might well parallel size even though steric bulk alone may not be the *principal* source of this effect.

Insofar as silica gel or alumina presents a relatively polar surface to approaching molecules, the substituent "effectiveness scale" that seems to offer the best means for fitting the chromatographic behavior of carbamate diastereomers to an ease of approach type model is a "hydrophobic" scale. Bearing in mind that backbone rigidity has a marked chromatographic consequence, it appears that the "warding off" effect increases in the sequence methyl < phenyl ≈ ethyl < *n*-propyl < *tert*-butyl ≪ trifluoromethyl < heptafluoropropyl. The relative magnitudes of these "warding off" effects cannot be quantitatively ascertained for it must be borne in mind that the magnitude of such an effect is probably not independent of the other substituents present.

Introduction of trifluoromethyl groups onto the carbamate backbone has not seriously altered solution conformations judging by the consistent chemical shift differences observed between diastereomers. Trifluoromethyl groups are known to be quite hydrophobic[17] and appear to be extremely effective in "warding off" the polar adsorbent and reducing the probability that the carbamate will be adsorbed from the face presenting this group. This effect suffices to account for the "inverted" (from steric consideration only)[18] elution orders and for the hastened elution of both diastereomers relative to those of the nonfluorinated analogues. When the probability for adsorption from the trifluoromethyl bearing face is low, it makes little additional difference as to the identity (i.e., alkyl vs. aryl) of the second group of this face (provided that it is relatively nonpolar). The probability that adsorption will occur from the opposite face is somewhat greater and is significantly influenced by the identity of the second group. Thus, the overall adsorption probability for the trifluoromethyl carbamates is higher for the diastereomer having the aryl groups trans to one another. The improvements in chromatographic separability of the diastereomers that attend the trifluoromethyl substituents is presumed to stem largely from the increased degree of conformational control that this group confers through enhanced carbinyl hydrogen bonding.[6] The 9-anthryl substituted carbamates **10a,b** and **11a,b** are anomalous in that the usual elution order is inverted, presumably as a consequence of the greater "warding off" ability of 9-anthryl than trifluoromethyl. Elution order is normal for **14a,b** since the (now) greater hydrophobicity of heptafluoropropyl dominates the effect of the 9-anthryl substituent. These carbamate diastereomers show no anomalies in the chemical shift difference–stereochemical correlation, suggesting that no appreciable alteration of backbone conformation has occurred.

The present model says nothing about the site(s) of interaction of the adsorbent with the carbamate diastereomers. Although one might intuitively expect the carbonyl oxygen to be the major site for interaction with the adsorbent, the observation (subsequently to be discussed) that the αs and K's increase in the order acidic < neutral < basic alumina and the much reduced K' (and α) values for analogous N-methylated carbamate diastereomers leads to speculation that perhaps the hydrogen on nitrogen plays some role in the adsorption process. Identification of the site(s) at which adsorption occurs is of interest and importance even though the present model does *not* hinge upon explicit identification of this site. However, the model does imply that adsorption occurs principally in the central polar region of the carbamate between the chiral carbons.

Table II. Eu(fod)$_3$ Induced Chemical Shift Gradients for Aryl Alkyl Carbamates



	Gradient,[a] ppm/mol Eu(fod)$_3$ in CCl_4		
R	H_a	H_b	H_c
CF_3	4.3	2.6	8.7
CH_3	5.7	3.7	7.4

[a] Gradients are presented as least-squares slopes of the essentially linear portion of the curves noted for Eu(fod)$_3$: substrate ratios of less than 0.2. The correlation coefficients of the least-squares slopes range from 0.999 to 0.988.

The chromatographic data in Table I were obtained using a 1 × 26 cm column packed with Woelm 18–32 μ neutral alumina and benzene eluent. The activity and increased surface area of this adsorbent cause the K' values reported to be somewhat larger than those observed on the adsorbent (Brinkmann 63–200 μ neutral alumina) used in the large (5 × 120 cm) multigram columns. However, α values are relatively unchanged. Acidic alumina affords smaller αs and K's than does neutral alumina of the same brand and particle size whereas basic alumina affords increased α and K' values. Silica gel is usually less effective than alumina for separating these diastereomers, although there are exceptions to this generalization. Variation of adsorbent or solvent has thus far produced no change in elution order. Increases in the polarity of the eluting solvent hastens elution and lessens α. Presumably, this latter diminution stems from less effective conformational control (by intramolecular carbinyl hydrogen bonding).

Solution Conformations. From magnitudes of the Eu(fod)$_3$ induced chemical shift gradients [ppm/mol Eu(fod)$_3$] shown in Table II, it is evident that both the carbinyl and methine hydrogens are near the site of Eu(fod)$_3$ coordination, the carbonyl oxygen.[19–21] The effect of the electronegative trifluoromethyl is to enhance the degree of CHB and to decrease the extent of coordination by Eu(fod)$_3$ to carbonyl oxygen. Enhanced CHB is noted in Table II by the relatively larger gradients for the carbinyl than for the methine proton when R is trifluoromethyl rather than methyl. Similarly, a reduced coordination level is indicated by the lesser methine and methyl (i.e., H_b) gradients for the fluorinated carbamates relative to the nonfluorinated analogues. This inference is strengthened by the results of competition experiments on structurally similar carbamates.[6] Significantly, the erythroid and threoid diastereomers do not preceptably differ in their Eu(fod)$_3$ gradients as evidenced by representative data in Table III. This suggests that Eu(fod)$_3$ does not discern appreciably between diastereomers and is consistent with the two diastereomers having solution conformations similar to **2a,b** (or the weighted, time-averaged equivalent) and the Eu(fod)$_3$–oxygen bond lying essentially along the carbon–oxygen axis of the carbonyl group. It cannot be rigorously inferred that Eu(fod)$_3$ binds differently to the carbamates

Table III. Eu(fod)$_3$ Induced Chemical Shift Gradients and Chemical Shift Data for Diastereomeric Pairs of Carbamates

			Gradient,[d] ppm/mol Eu(fod)$_3$ in CCl$_4$						Chemical shift data[f]								
Compd	R	R$_1$	H$_a$	H$_b$	H$_c$	Elution order	α[e]	δ_a	δ_b	δ_c	$\Delta\delta_a$[g]	$\Delta\delta_b$[g]	$\Delta\delta_c$[g]	δR[h]	δR$_1$[h]	$\Delta\delta$RR$_1$[i]	$\Delta\delta$R$_1$,R[j]	Mp,[k] °C
22a	Methyl	Ethynyl	3.80	1.05	3.41	High R_f	1.13	5.66	1.65	5.45	−0.02	−0.01	0.01	1.49	2.49	−0.02	0.05	116
22b	Ethynyl	Methyl	3.69	1.09	3.26	Low R_f		5.68	1.66	5.44				2.44	1.51			116
23a	Ethyl	Ethynyl	4.90	1.85	4.55	High R_f	1.21	5.68	1.65	5.33	−0.02	−0.04	0.00	0.96	2.48	−0.10	0.02	91
23b	Ethynyl	Ethyl	4.78	1.88	4.29	Low R_f		5.70	1.69	5.33				2.46	1.06			119
24a	n-Butyl	Ethynyl	2.44	0.89	2.44	High R_f	1.27	5.68	1.63	5.36	−0.02	−0.03	0.01	0.88	2.49	−0.06	0.04	110
24b	Ethynyl	n-Butyl	2.22	1.28	2.32	Low R_f		5.70	1.66	5.35				2.45	0.94			95
8a	α-Naph	CF_3	4.40	2.50	8.80	High R_f	1.56	5.54	1.54	7.03	−0.04	0.08	0.01					139–140
8b	CF_3	α-Naph	4.30	2.60	8.70	Low R_f		5.58	1.46	7.02								123

[d] Gradients are presented as least-squares slopes of the essentially linear portion of the curves noted for Eu(fod)$_3$:substrate ratios of less than 0.2. The correlation coefficients of the least-squares slopes range from 0.998 to 0.989. [e] These carbamates were chromatographed on silica gel with CH_2Cl_2–hexane (7:3). [f] Chemical shifts (δ) are in parts per million downfield of Me$_4$Si. [g] $\Delta\delta = \delta_{\text{high } Rf} - \delta_{\text{low } Rf}$. [h] For ethyl and n-butyl substituents, δ refers to the chemical shift of the methyl protons distal to the carbinyl carbon. [i] $\Delta\delta$RR$_1$ refers to the chemical shift difference between the entry for R of diastereomer a and the entry for R$_1$ of diastereomer b, for a given pair of diastereomers. [j] $\Delta\delta$R$_1$,R refers to the chemical shift difference between the entry for R$_1$ of diastereomer a and the entry for R of diastereomer b, for a given pair of diastereomers. [k] All the carbamates in this table gave satisfactory elemental analyses and mass spectra.

than does alumina (or silica) simply because the shift reagent shows no marked preferential binding to one diastereomer whereas the adsorbents do. "Warding off" effects by substituents may be rather different toward Eu(fod)$_3$ than for an adsorbent.

Table III also contains chromatographic data for the diastereomeric carbamates derived from some acetylenic alcohols. The usual correlations between NMR spectral differences, elution order, and stereochemistry are observed for diastereomeric pairs **22a,b–24a,b.** One infers that ethynyl groups are more effective in warding off the adsorbent than methyl, ethyl, or n-butyl groups.

Shift reagent studies similar to those just described show that there is no notable alteration in backbone conformation between diastereomers **17a,b** and **18a,b,** even though an *inversion* in elution order of the diastereomers occurs. For these diastereomers, the Eu(fod)$_3$ gradients for each of the erythroid and threoid isomers indicate the carbinyl and methine protons to be in close proximity to the carbonyl oxygen, and the alkyl substituents to be equivalently disposed with respect to the backbone structure.

Conformational Equilibria. The Eu(fod)$_3$ experiments conducted on compounds appearing in Tables II and III were carried out at 220 MHz and at 27 °C. In the absence of shift reagent there were no spurious signals in the spectra of any of these diastereomers. However, upon incremental addition of Eu(fod)$_3$, all diastereomers so investigated gave rise to minor resonances, which were taken to indicate the "freezing out" of a dynamic equilibrium between the Z and E rotamers owing to hindered rotation about the carbonyl carbon–nitrogen bond.

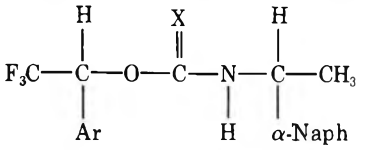
In the absence of shift reagent, the Z rotamer is more heavily populated than the E rotamer. However, the latter is

Z E

coordinated more strongly by Eu(fod)$_3$, and with increasing amounts of shift reagent, the observed time averaged ratio of Z:E rotamers progressively diminishes. Because of its greater binding toward Eu(fod)$_3$, the minor E rotamer shows larger gradients than the Z rotamer at the concentrations of shift reagent utilized. These data are readily rationalized on steric and electronic grounds. Coordination to Eu(fod)$_3$ occurs most readily when the larger group on nitrogen (the chiral assembly) is trans anti-periplanar to the carbonyl oxygen and no competing CHB from the methine hydrogen is possible. Extrapolation of the observed Z:E ratios to zero Eu(fod)$_3$ concentration indicates an initial ca. 90:10 rotamer mixture for all the carbamates so investigated. Apparently, the nature of the alkoxyl portion of the carbamate normally has little effect upon this ratio. Owing to the minor amount of the E rotamer originally present and its spectral similarity to the Z rotamer, the presence of the E rotamer can seldom be detected without the addition of shift reagent.

The population of the E rotamer has possible implications with regard to the chromatographic separability to the diastereomeric carbamates. To whatever extent coordination to Eu(fod)$_3$ resembles the adsorption process, one might expect the E rotamers to be more strongly adsorbed than the Z rotamers. Moreover, the E rotamer may have opposite relative placements of the backbone substituents and might consequentially tend to invert the elution orders of diastereomers relative to that which would be observed were only the Z rotamers populated. Data concerning E rotamer conformation

Table IV. Comparative NMR and Chromatographic Data (Carbamate vs. Thiocarbamate)



No.	X	Ar	$\Delta\delta^a$ (CH_3)/ field sense	High R_f	α
26	S	Phenyl	0.08 low	Erythroid	1.29
4	O	Phenyl	0.05 low	Erythroid	1.58

$^a \Delta\delta = \delta_{CH_3 \text{ high } R_f} - \delta_{CH_3 \text{ low } R_f}$.

are difficult to extract from shift reagent studies since most *E* resonances are buried beneath the major *Z* resonances.

To determine the solution and chromatographic effects of less preferential population of *Z* rotamers **2a,b**, the diastereomeric carbamates **25a,b** derived from the chloroformate of (±)-1-(1-naphthyl)-2,2,2-trifluoroethanol and (*S*)-(−)-*N*-methyl-α-phenylethylamine were prepared and studied.

Both N-methylated diastereomers give NMR evidence of hindered rotation at 28 °C and 100 MHz in the *absence* of shift reagent and the relative ratio of the *E* and *Z* rotamers is nearly unity. Under chromatographic conditions that easily separate the diastereomers of the nonmethylated carbamates, the N-methylated diastereomers elute rather more rapidly and give little separation (compare, for example, the α value of carbamate **4** with that of the N-methylated analogue, 1.58 vs. 1.15). Use of less polar solvents increases the α value somewhat, but not to the magnitude of the nonmethylated analogues. The chromatographic behavior of the N-methylated carbamate diastereomers further supports the view that the chromatographic separability of these diastereomers is linked to the extensive population of one type of solution conformation. Finally, as an additional test of the observed chromatographic patterns, a pair of diastereomeric trifluoromethyl thiocarbamates **26a,b** were synthesized[23] and chromatographed. It may be seen (Table IV) that replacement of carbonyl oxygen with sulfur affects neither elution order (i.e., erythroid is first eluted) nor sense of NMR spectral differences. However, the thiocarbamates do not separate as well as their carbamate analogues.

In summary, we note that the preceding chromatographic rationale offers a foundation upon which the rational design of improved chromatographic resolving agents may be based. Clearly, the use of CDA which afford conformationally restricted diastereomeric derivatives will facilitate the chromatographic separation of these derivatives as will incorporation of substituents such as perfluoroalkyls that are capable of translating their necessarily different stereochemical arrangement into differential probabilities of adsorption for the diastereomers.

Experimental Section

^1H NMR spectra were obtained with Varian Associates A-60A, A56-60, HA-100, or HR-220 instruments. Chromatographic data in Table I were obtained upon Woelm 18–32 μ neutral alumina using benzene eluent. In many cases crude reaction mixtures were preparatively separated as described on 5 × 120 cm columns of Brinkmann 63–200 μ neutral alumina, again using benzene eluent. In all cases the effluent was monitored at 280 nm.

Carbamates. All carbamates[25] used in this study were prepared via one of two procedures.

Procedure A. A mixture of racemic alcohol (ca. 4.5 mmol), (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.89 g, 4.5 mmol), and *N,N*-dimethylethanolamine (1 wt %) in benzene (50 mL) was heated to 80 °C for 24–36 h, at which time the isocyanate band at 2260 cm^{-1} had mostly disappeared. Longer reflux times did not substantially increase yields, but rather caused cracking of the product. The mixture was chromatographed directly upon a preparative HPLC system using benzene–alumina. The effluent was monitored at 280 nm.

Procedure B. To a solution of phosgene (1.47 g, 15 mmol) in 15 mL of dry toluene[24] cooled to −5 °C was added dropwise a solution of racemic carbinol (ca. 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) in 25 mL of dry toluene.[24] After addition was completed, stirring was continued for 30 min at 0 °C. The amine hydrochloride was then removed by filtration under nitrogen and the filtrate concentrated at reduced pressure (ca. 50 mmHg) with heating (40–50 °C).

The crude chloroformate and 25 mL of CH_2Cl_2 were then placed in a three-necked round-bottom flask equipped with overhead stirrer, nitrogen inlet, and vented dropping funnel. A solution of triethylamine (0.76 g, 7.5 mmol), (*R*)-(+)-1-(1-naphthyl)ethylamine (1.28 g, 7.5 mmol), and 25 mL of CH_2Cl_2 was then added dropwise and stirring was continued overnight at room temperature. The reaction mixture was washed with two 50-mL portions of 3 N HCl and the organic layer dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated (ca. 50 mmHg, 30 °C) and the mixed carbamates chromatographed as described.

Acknowledgment. This work has been supported in part from grants from the National Institutes of Health and the National Science Foundation.

Registry No.—**4a**, 61787-33-5; **4b**, 61787-34-6; **5a**, 61787-35-7; **5b**, 61787-36-8; **6a**, 61787-37-9; **6b**, 61787-38-0; **7a**, 61787-39-1; **7b**, 61787-40-4; **8a**, 61848-81-5; **8b**, 61848-82-6; **9a**, 61787-41-5; **9b**, 61787-42-6; **10a**, 61787-43-7; **10b**, 61787-44-8; **11a**, 61787-45-9; **11b**, 61787-46-0; **12a**, 61848-83-7; **12b**, 61848-84-8; **13a**, 61787-47-1; **13b**, 61787-48-2; **14a**, 61787-49-3; **14b**, 61787-50-6; **15a**, 61787-51-7; **15b**, 61787-52-8; **16a**, 61787-53-9; **16b**, 61787-53-9; **17a**, 61787-54-0; **17b**, 61787-55-1; **18a**, 61787-56-2; **18b**, 61787-57-3; **19a**, 61787-58-4; **19b**, 61787-59-5; **20a**, 61787-60-8; **20b**, 61787-61-9; **21a**, 61787-62-0; **21b**, 61787-63-1; **22a**, 61787-64-2; **22b**, 61787-65-3; **23a**, 61787-66-4; **23b**, 61787-67-5; **24a**, 61787-68-6; **24b**, 61787-69-7; **25a**, 61787-70-0; **25b**, 61787-71-1; **26a**, 61787-72-2; **26b**, 61787-73-3; (+)-1-(1-naphthyl)-2,2,2-trifluoroethanol, 17556-44-4; (*S*)-(−)-*N*-methyl-α-phenylethylamine, 19131-99-8.

Supplementary Material Available. Spectral data (NMR, IR, and mass spectra) as well as elemental analyses (15 pages). Ordering information is given on any current masthead page.

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(2) W. H. Pirkle and R. W. Anderson, *J. Org. Chem.*, **39**, 3901 (1974).
(3) For example, of approximately 1200 "practical resolutions" listed in S. H. Wilen, "Table of Resolving Agents and Optical Resolutions", University of Notre Dame Press, Notre Dame, Ind., 1972, and occurring between 1950 and 1970, only 35 are indicated to involve chromatographic techniques. Not all of these involve the separation of diastereomers but include the use of chiral stationary phases such as quartz or cellulose acetate.
(4) Diastereomeric carbamates derived from 1-phenylethyl isocyanate have previously been separated on an analytical scale by thin layer and gas chromatography.[13,14] This reagent has been used to convert most of the carbinols appearing in Table I into diastereomeric carbamates. Without exception, these diastereomers do *not* separate as well as the 1-naphthylethyl analogues. However, elution orders and senses of NMR nonequivalence are the same for both series of diastereomers.
(5) Where absolute configurations had previously been assigned (see W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press, New York, N.Y., 1974, for a useful compilation) polarimetry could be used. In most instances, however, configurations were determined by NMR (using chiral solvating agents of known configuration) and have not been reported previously. Although a more complete description of this method will appear elsewhere, our earlier report [W. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89**, 4585 (1967)] is illustrative of the technique.
(6) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41**, 801 (1976).
(7) These extremes can be realized during the separation of enantiomers upon either an achiral adsorbent using a chiral eluent or a chiral adsorbent using an achiral eluent. Both types of resolutions are known.
(8) For an excellent and extensive review of the separation of diastereomers by gas chromatography, see E. Gil-Av and D. Nurok, *Adv. Chromatogr.*, **10**, 99 (1975). Possible mechanisms of such separations are thoroughly discussed. We wish to emphasize that several of the separation mechanisms considered in this paper are antedated by the work of others even though such work is largely confined to gas chromatography.
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(13) W. Freytag and K. H. Ney, *J. Chromatogr.*, **41**, 473 (1969).
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(15) Helmchen believes[9] that, in view of the distances involved, the C substituents do not interact with the A substituents.
(16) The consequences of conformational immobility have been recognized and demonstrated[11b,c] insofar as diastereomeric amides derived from some chiral cyclic acids and chiral cyclic amines separate better than those similarly derived from acyclic components.
(17) M. Hudlicky, "Chemistry of Organic Fluorine Compounds", Macmillan, New York, N.Y., 1961, p 304, and references cited therein.
(18) When the diastereomeric carbamates derived from (±)-1,1,1-trifluoro-3,3-dimethyl-2-butanol and (+)-1-(1-naphthyl)ethylamine are chromatographed, the diastereomer which has *tert*-butyl and α-naphthyl on the *same* face (erythroid) is *first* eluted. Since the van der Waals radius of *tert*-butyl is larger than trifluoromethyl (6.1 vs. 5.1 Å respectively), this elution order reflects that the greater "warding off" effect of the trifluoromethyl group is not simply steric in nature, but has other origins.
(19) C. S. Springer, Jr., S. R. Tahny, and M. Pickering, *J. Am. Chem. Soc.*, **95**, 6227 (1973).
(20) R. A. Bauman, *Tetrahedron Lett.*, 419 (1971).
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(22) H. Kessler and M. Molter, *J. Am. Chem. Soc.*, **98**, 5969 (1976).
(23) Thiocarbamates with Ar = α-naphthyl and Ar = 9-anthryl were also synthesized. Although NMR and chromatographic properties appear to be analogous to those of the corresponding carbamates, the instability of these thiocarbamates did not permit thorough characterization.
(24) Diethyl ether, tetrahydrofuran, and methylene chloride as well as toluene may be used as solvents with essentially *no* diminishment in overall yield.
(25) Ethynyl carbamates were prepared by C. Boeder.

Solid Phase and Solution Photochemistry of Coumalate Esters

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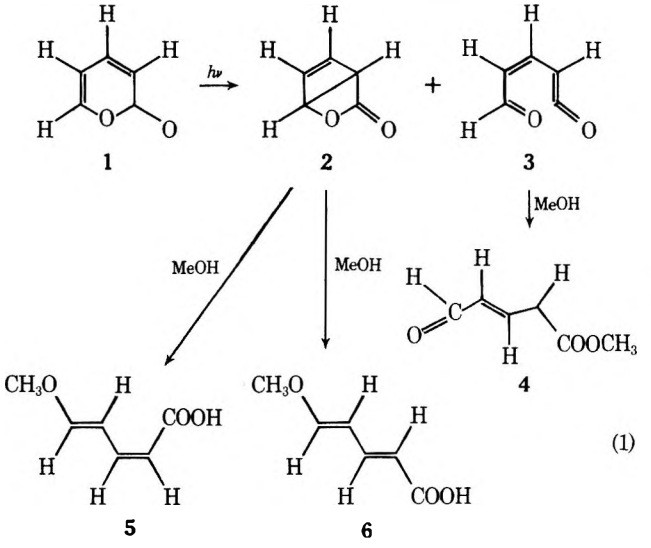
Photochemical reactions of coumalic acid (**12**) and its methyl, isopropyl, and benzyl esters have been investigated in solution and in the solid phase. In solution the photochemistry has been carried out in hydroxylic and nonhydroxylic solvents as well as in ethyl bromide. In the solid phase, the reaction has been studied in a potassium bromide matrix and as a sandwich between quartz plates. A particularly interesting effect of KBr, suggested to be a heavy atom effect of the matrix, has been observed in the photochemical reactions of coumalate esters.

The photochemistry of α-pyrone (**1**) and its derivatives has been the subject of several studies and the systems have proven to be rich in variation.[1-10] In spite of their apparent complexity, however, all the observed unimolecular primary photoproducts arise from the critical intermediates bicyclic lactone **2** and ketene **3** (eq 1). Thus, irradiation of α-pyrone

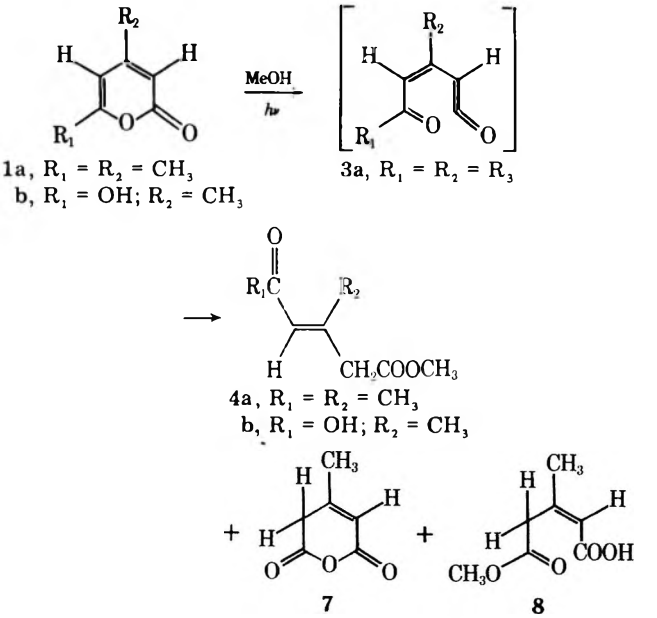


1 2 3 4 5 6 (1)

in ether at 300 nm produces only isolable **2** in quantitative yield[1-3] while in methanol under similar conditions, the three noncyclic products **4**, **5**, and **6** result. Compound **4** has been shown to derive from ketene **3**, whereas **5** and **6** are from the photolactone **2**.

Intermediate ketenes like **3** have been the subject of several studies. The current view is that, in the case of α-pyrone[2,3,9] and certain properly substituted ones,[5,6] such ketenes form, though in apparently analogous cases[8] ketenes seem not important. Thus irradiation of 4,6-dimethyl-2-pyrone (**1a**) in methanol produces **4a** through ketene **3a**[2], while 4-hydroxy-6-methyl-2-pyrone (**1b**), when irradiated in methanol, produces **4b** (in tautomeric form) in addition to anhydride **7**. The half-ester **8** which originates from lactone **2b**[6] is also formed, Scheme I. The analogous 4-methoxy-6-methyl-2-pyrone (**1c**),

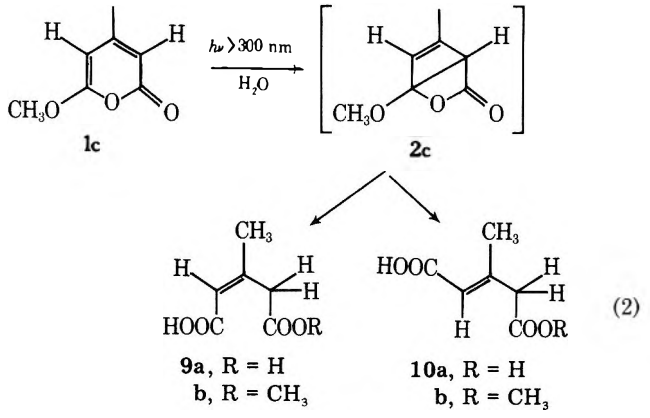
Scheme I



7 8

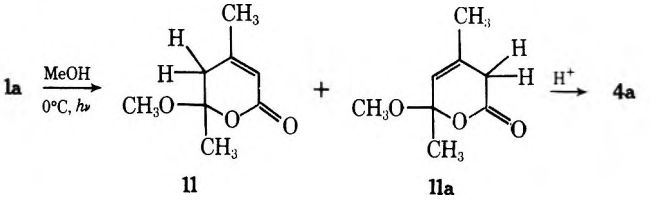
when irradiated in water at 300 nm, produces the half-esters **9a** and **10a** and the corresponding diacids **9b** and **10b**. Both these products are said to originate from lactone **2c**[5] (eq 2).

* Fellow of the Alfred P. Sloan Foundation, 1971-1976.
† Submitted in partial fulfillment of the requirements for the Ph.D. degree, University of Toledo, 1976. Deceased March 21, 1977.



(2)

Chapman and McIntosh[8] disagree that ketene **3a** is formed from **1a** in methanol, claiming formation of two acid-sensitive isomeric lactones, **11** and **11a**. Addition of acidic methanol to **11** and **11a** produces **4a**.

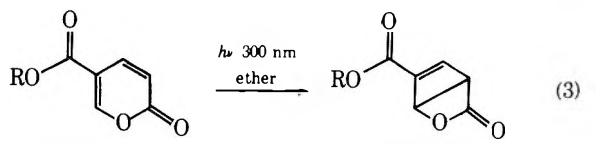


Still another complication is the observation of dimerization reactions of α-pyrones which occurs from triplet states of α-pyrone derivatives. Thus cyclic adducts have been isolated both from direct and from sensitized reactions of α-pyrone,[4,11] in triplet state reactions.

In this paper we report on the photochemistry of coumalic acid (**12**) and its esters, both in solution and the solid phase. As part of a series of model studies, we were interested in the effect of carboxylate residues on the photoreactions of pyrone derivatives.

Results and Discussion

The photochemistry of coumalic acid and its ester derivatives has been studied in solution using hydroxylic and nonhydroxylic solvents, as well as heavy atom solvents, such as ethyl bromide. These reactions were also studied in the solid phase, with the coumalate either a suspension in a potassium bromide matrix or sandwiched between two quartz plates. The observed results were dependent on the physical state and the solvent as well as on the wavelength of irradiating light. For example, methyl coumalate (**12a**) in ether, when irradiated at 300 nm, produced 5-carbomethoxy-3-oxabicyclo[2.2.0]-hex-5-en-2-one (**13a**) quantitatively (eq 3).



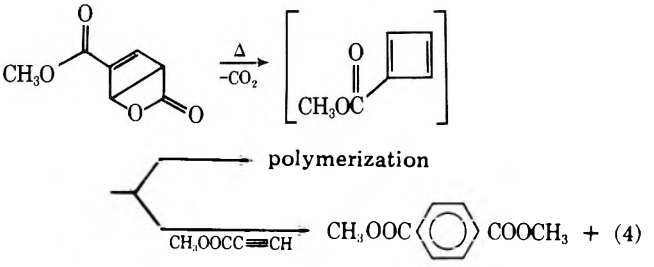
(3)

Lactone **13a** was stable when compared to the parent photo-α-pyrone **2** and could be stored indefinitely and even bulb to bulb distilled at 40 °C and 3 mm. During this distillation **3a** only partially (≈10%) reverted to methyl coumalate. Isopropyl coumalate (**12b**) behaved similarly as did benzyl coumalate (**12c**). In the latter case, however, some side chain photodecarboxylation also occurred.

The spectral properties of isolated photopyrones **13a–c** are shown in Table I.

The mass spectrum of **13a** revealed a base peak at *m/e* 110, formed by loss of CO_2 from the parent compound. Since the loss of CO_2 is more likely from the lactone group than the ester, the ion at *m/e* 110 is likely the cyclobutadiene methyl carboxylate ion or a ring-opened isomer. The comparable mass spectrum of methyl coumalate places the base peak at *m/e* 126. This same ion, in the mass spectrum of **13a**, is minor (10%) indicating that **13a** did not rearrange to methyl coumalate under the conditions where the mass spectrum was recorded.

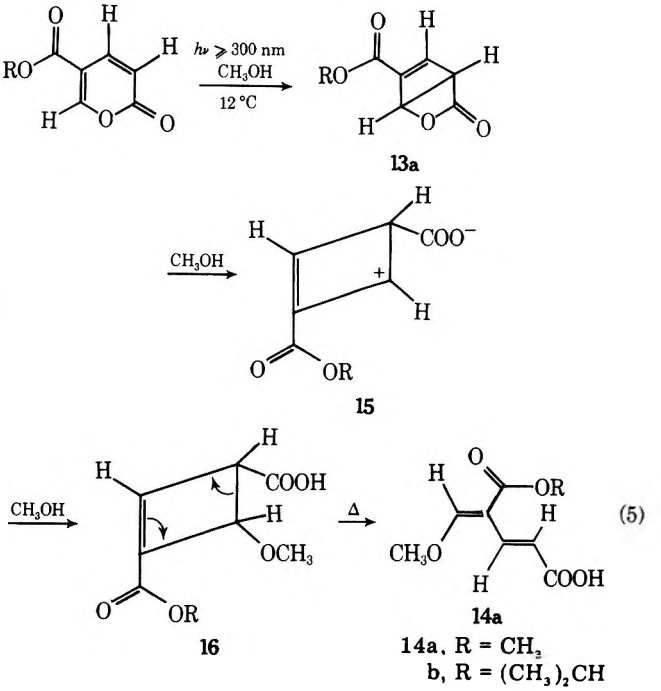
The loss of CO_2 from **13a** is also observed when it is heated in a melting point capillary tube or between KBr plates at 110 °C. The NMR spectrum of the thermal product from **13a** contains a strong and broad signal at 3.80 ppm indicating the presence of polymeric methyl ester protons. These likely arise from cyclobutadiene derivatives which, if formed, do not survive the experimental conditions and are polymerized in an unidentified manner (eq 4).



(4)

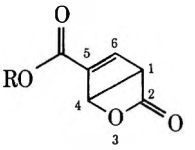
Several attempts were made to trap the theorized cyclobutadiene derivatives produced in the thermolysis of **13a** by carrying out the reaction in the presence of active dienophiles. Though dimethyl phthalate esters were discovered among the products, the results are still premature and further investigations are needed.

When methyl coumalate is irradiated in methanol, similar reactions occur. However, secondary thermal reactions cause complications and none of the primary photoproducts are stable in methanol at room temperature. Thus, **13a**, the ring closure product of methyl coumalate, isolated from photolysis in ether, adds methanol thermally to form the dienoic acid **14a** via secondary intermediates **15** and **16** (eq 5). In our hands



(5)

Table I. Spectral Properties of Photopyrones 13a–c

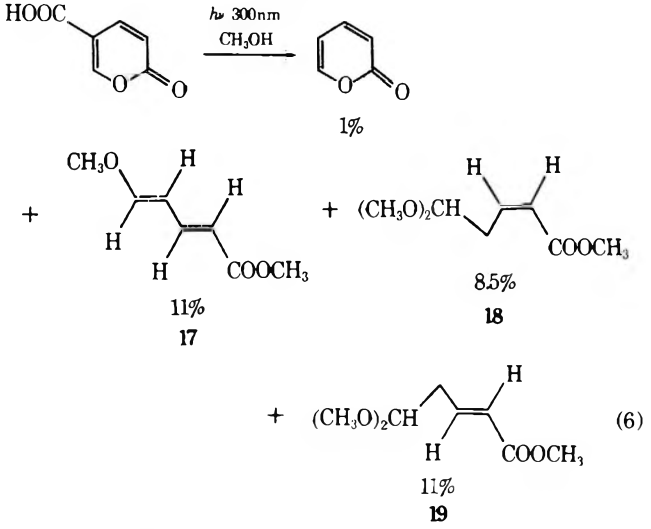


Compd	R	Chemical shifts, ppm[a] C_1	C_4	C_6	Coupling constants, Hz $J_{1,4}$	$J_{1,6}$	$J_{4,6}$	IR, cm^{-1} [b] C=O lactone	C=O ester
13a	Methyl 3.90	5.63	4.58	7.41	2	4	1	1825	1725
13b	Isopropyl 1.29, 5.13	5.58	4.52	7.35	2	4	1	1825	1722
13c	Benzyl 7.41, 5.79	5.52	4.45	7.35	2	4	1	1823	1720

[a] In $CDCl_3$. [b] Thin film on KBr plates.

there was no evidence favoring formation of any intermediate but bicyclic lactone **13a** from methyl coumalate when irradiated in methanol. Thus we obtained no evidence for either the ketene or Chapman–McIntosh intermediates.

We did not study the photochemistry of coumalic acid in ether or benzene owing to solubility problems. However, in methanol its photochemistry, too, proved to be rich and varied. At 300 nm the major photoproduct from irradiation was a decarboxylation product, α-pyrone, the analogue of the thermal reaction by which α-pyrone is prepared.[12] Consequently, the products produced in methanol were those from photoreaction of α-pyrone except that the methanol solution of coumalic acid was acidic enough to produce acetals rather than aldehydes. The products isolated from irradiation of coumalic acid in methanol are shown in eq 6. We judge that



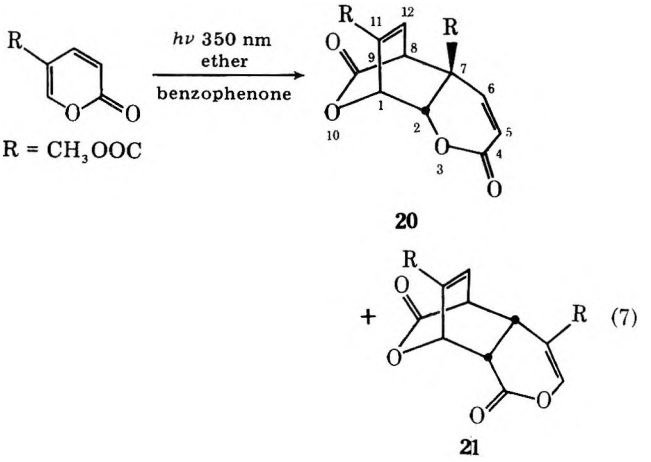
(6)

ketene intermediates are involved in formation of **18** and **19** but have no definitive proof.

Potassium bromide matrix photochemistry is possible[13–15] owing to the excellent transparency of this medium. Thus irradiation of all the coumalates, pressed in KBr disks, produced markedly different results. When irradiated at 254 nm in KBr, the coumalate esters, as well as coumalic acid itself, lost CO_2. The infrared spectrum of methyl and benzyl coumalate before and at selected periods after irradiation demonstrated that both the ester and lactone carbonyls serve as the source of CO_2. Though ring closure to photolactones is not expected from coumalates at short irradiating wavelengths, it is surprising that ring closure could not be observed when coumalates were irradiated at longer wavelengths (300 and 350 nm) in a KBr matrix.

The rate of CO_2 loss from the various coumalate esters differed and was dependent on the attached alkyl or aryl group. Thus the loss of CO_2 from the side chain of benzyl coumalate, when irradiated in KBr at 254 nm, is faster than is the loss of CO_2 from the side chain of methyl coumalate. The same observation was made when a 300-nm light was used.

When irradiated at 350 nm in a KBr matrix, no CO_2 is produced from methyl coumalate; instead, [4 + 2] dimeric adducts **20** and **21** are formed. These dimers are the same as those isolated from benzophenone sensitized irradiation of methyl coumalate in ether or from irradiation in ethyl bromide, a known heavy atom solvent (eq 7). These dimers are triplet state products.



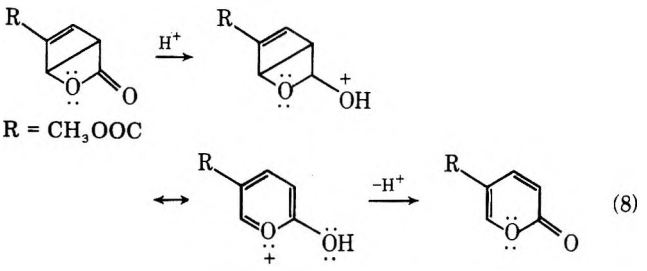
(7)

The source of CO_2 from methyl coumalate irradiation is not methyl coumalate itself, but is instead the dimers **20** and **21**. This can be shown by two studies. In the first, dimers **20** and **21**, prepared from benzophenone sensitized reaction of methyl coumalate in ether at 350 nm, are isolated and then pressed into KBr matrix and irradiated at 300 nm. CO_2 evolution can be demonstrated to be similar in rate to that obtained by the direct irradiation of methyl coumalate under identical conditions. In the second study, irradiation of methyl coumalate at 350 nm produces dimerization which can be demonstrated by the disappearance of the diene double bond stretching frequency at 1550 cm^{-1}. At 350 nm, however, almost no CO_2 is evolved. When irradiation is continued at 300 nm using the same pellet, CO_2 evolution begins though the dimerization continues at the same rate. Benzyl coumalate behaves simi-

larly when irradiated at 350 nm as does isopropyl coumalate when irradiated in a KBr matrix under similar conditions.

The fact that, in KBr matrix, none of the photochemistry observed in solution is observed is curious, and at least two explanations are possible. The first is that, in a KBr matrix, the derivatives of the photopyrones are unstable and revert back to the starting material immediately after formation, thus escaping detection. The second is that the excited state multiplicity of the coumalates is different in solution than in a KBr matrix.

To examine the first of the above postulates a small amount of **13a** was sandwiched between two KBr plates and irradiated. The IR spectrum of the ester was recorded periodically for 120 min. During this period the carbonyl band at 1825 cm^{-1} slowly disappeared and the spectrum completely changed to that of methyl coumalate. A KBr matrix of **13a** gave similar results rapidly enough so that no photopyrone could be detected at all. We think that the slightly acidic condition of the plate causes isomerization of **13a** to **12a** (eq 8).



(8)

Examining the second postulate, heavy atom solvents have been shown to enhance forbidden $t_1 \leftarrow s_1$ intersystem crossing transitions.[16-23] The effects that can be observed spectroscopically are an increase in the extinction coefficient in the absorption spectra, an increase in the quantum yield of 0–0 band in the phosphorescence spectra, and a decrease in the lifetime of phosphorescence. External heavy atom effects[18-20,23] and internal heavy atom effects[16,23] have been investigated extensively with a number of photochemical processes in solution but the heavy atom effect of alkali halides in solid phase[25-29] has not been explored as extensively.

The UV spectra of coumalate esters in a KBr matrix are similar to the respective solution spectra (Figure 1), with the exception of a slight line broadening and an accompanying red shift of the peaks at 246 and 298 nm, to 251 and 305 nm, respectively. (Similar observations have been made by Pitts[26] and by Drickamar[15] in their studies involving anthracene.) Enhancements of the extinction coefficients of the 246- and 298-nm bands are to be expected if a heavy atom effect is effective, but these effects cannot be quantitatively assessed in a solid KBr matrix because of concomitant light scattering from the KBr surface. The latter is confirmed by the observation that the extinction coefficient of the band or at shorter wavelength (246 nm) is decreased more than that in the longer wavelength region (298 nm) (Figure 1). When the UV spectrum of methyl coumalate was recorded in a methanol solution containing KBr a small increase (7%) in the extinction coefficient was observed for the 298-nm peak.

Although the investigation of the UV spectra of coumalate esters and, in particular, methyl coumalate did not give sufficient evidence for an external heavy atom effect, the chemical evidence favoring a heavy atom effect is significant. Thus when methyl coumalate was irradiated in ethyl bromide (a heavy atom solvent), formation of the same [4 + 2] dimeric adducts as those observed in the benzophenone sensitized reaction of methyl coumalate in ether resulted. Even though the photolactones are not stable in a KBr matrix, the same distribution of dimeric products results in ethyl bromide solution, in ether with benzophenone sensitizer, or in a matrix

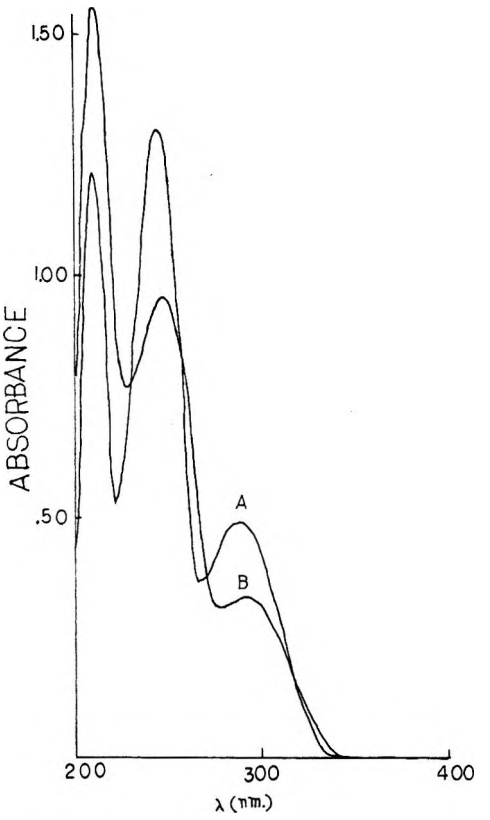


Figure 1. (A) UV spectrum of benzyl coumalate (1.32×10^{-4} M) in methanol, λ_{max} 288 nm (ϵ 3700) and 246 (9800). (B) UV spectrum of benzyl coumalate (1.32×10^{-3} M) in KBr matrix, λ_{max} 292 nm (ϵ 1800) and 247 (5250).

of KBr. We think it compelling and suggest that methyl coumalate, irradiated in KBr matrix, may well be *the first conclusive example of the external heavy atom effect observed in solid KBr*.

There are at least four pieces of evidence to support this statement. First, irradiation of methyl coumalate in crystalline form did not produce dimers. Second, irradiation of methyl coumalate sensitized with benzophenone produced dimers which are necessarily derived from its triplet states and these dimers were the same as those produced from irradiation of methyl coumalate in a KBr matrix. Third, irradiation of methyl coumalate in ethyl bromide, a known heavy atom solvent, produced the same dimers as those observed in the benzophenone sensitized reaction and those obtained from irradiation of methyl coumalate in a KBr matrix. Fourth, irradiation of methyl coumalate in ether produced a nondimeric product derived from a singlet excited state.

In conclusion, then, ether solutions of coumalate esters, when irradiated at 300 nm, produce corresponding ester derivatives of 3-oxabicyclo[2.2.0]hex-5-en-2-one. These products are derived from singlet excited states of coumalate esters. In contrast to their unsubstituted counterpart carboxylated photopyrones are stable at room temperature and can survive molecular distillation at reduced pressures. In hydroxylic solvents such as methanol, substituted photopyrones undergo thermal reactions to form the corresponding derivatives of 5-methoxy-2-*cis*-4-*trans*-pentadienoic acid. Coumalic acid itself, upon irradiation in methanol, behaved differently since it initially underwent photodecarboxylation to produce α-pyrone. Only the thermal chemistry was changed due to the acidic nature of the medium. Irradiation (300 nm) of coumalate esters, as well as coumalic acid, in a KBr matrix produces CO_2. In the case of coumalate esters, the CO_2 comes from [4 + 2] dimeric adducts of the type **20** and **21** rather than from

the esters themselves. In the case of methyl coumalate, the same dimers **20** and **21** are formed whether irradiation is carried out in a KBr matrix, sensitized with benzophenone, or in a heavy atom solvent, such as ethyl bromide. Since irradiation of the crystalline coumalate esters does not produce dimers, the dimers in KBr matrix are produced from a triplet excited state of the coumalate, likely brought about by the heavy atom.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 337 or 621 infrared spectrophotometer and are obtained as KBr plates unless otherwise noted. The proton magnetic resonance spectra (NMR) were obtained by using either a Varian Model A-60 or T-60A instrument and are relative to Me_4Si internal standard. In reporting NMR data, the following abbreviations are used: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, quin = quintet, and m = multiplet. The mass spectra were obtained using a Varian MAT Model CH7 mass spectrometer. Analytical gas–liquid chromatography (GLC) was carried out using a Varian Aerograph 1200 (column 8 ft × 18 in. UCON LB 10% on Chromosorb 60/90). For preparative work a Varian Aerograph 1800 (column 8 ft × 16 in. UCON LB 10% on Chromosorb W) was utilized. When necessary samples were also analyzed by a high-pressure liquid chromatograph (HPLC) Analab equipped with Tracor 500 pump. The column was packed with Partisil 10/25, no. 1144761.

Photochemistry. All the irradiation experiments were performed by one of the methods 1–4. Modifications were made when needed.

Method 1. A standard photochemical quartz immersion apparatus (capacity 350 mL) and a 450-W Hanovia medium-pressure lamp was surrounded by a cylindrical glass filter and submerged in a constant temperature bath maintained at 12 °C. Samples to be irradiated were dissolved in 350 mL of the appropriate solvent, degassed under nitrogen for 15–20 min, and irradiated, with stirring, under a nitrogen atmosphere.

Method 2. A merry-go-round irradiation apparatus (ACE) was submerged in a constant temperature bath and kept at 12 °C. Solutions to be irradiated were kept in 13 × 100 mm Pyrex culture tubes (capacity 8 mL) with Teflon-lined screw caps. All solutions were degassed with nitrogen, placed in the submerged irradiation apparatus, and photolyzed with a 450-W Hanovia medium-pressure lamp.

Method 3. A commercial air-cooled Rayonet photochemical reactor (Southern New England Ultraviolet Inc.) was utilized with 16 standard lamps which would be changed for 254, 300, or 350 nm radiation. The entire apparatus could be placed in a refrigerator if lower temperatures than ambient temperature were desired. Samples were irradiated in the same manner as mentioned in method 2.

Method 4. Solid samples were irradiated in potassium bromide (KBr) matrices prepared in the following manner. Approximately 0.5 mg (this amount varied depending on the extinction coefficient of a sample) was mixed with about 500 mg of anhydrous KBr and made into KBr, a pellet, in the usual manner.

Coumalic acid was prepared in 72% yield from DL-malic acid according to the method developed by Wiley and Smith.[29] Several recrystallizations were needed to obtain colorless crystals, mp 209–211 °C (lit.[29] mp 206–209 °C). α-Pyrone was prepared by a slight modification of the procedures developed by Zimmerman and co-workers.[12] The crude α-pyrone was a pink, oily material which, after distillation, resulted in 75% yield of a colorless liquid, bp 39–40 °C (3 Torr) [lit.[12] 110 °C (26 Torr)]. Methyl coumalate was prepared by the modification of the method used by Caldwell and co-workers[30] and purified by several recrystallizations from ether containing Norite. The yield was 13.8 g (33%), mp 70–71 °C (lit.[30] mp 73–74 °C). Isopropyl coumalate was prepared in 55% yield according to a modified procedure,[30] mp 43.5–44.5 °C (lit.[30] 44 °C).

Preparation of Benzyl Coumalate from Coumaloyl Chloride. A solution of 25 mL of anhydrous ether containing benzyl alcohol (2.05 g, 0.019 mol) and *N,N*-dimethylaniline (3.50 mL, 0.03 mol) was placed in a 100-mL round-bottom flask which was equipped with reflux condenser, drying tube, magnetic stirrer, and addition funnel. The entire coumaloyl chloride prepared above was dissolved in 50 mL of ether, filtered, and added slowly (~45 min) through the addition funnel. The solution was then allowed to reflux for 10 h.

The reaction mixture was worked up as follows. The brown reaction mixture was poured into 50 mL of water and the ether layer which separated was washed three times with 10 mL of 10% sulfuric acid, once with 10 mL of saturated sodium bicarbonate, and finally with 15 mL of water. It was then dried over anhydrous magnesium sulfate and filtered and solvent was evaporated. The resultant yellow, crystalline benzyl coumalate (40%) was recrystallized from hot ether containing Norite, mp 90–92 °C (lit.[30] 92 °C).

Coumaloyl Chloride. A 25-mL round-bottom flask was set up with reflux condenser, drying tube, and magnetic stirrer. Coumalic acid (2.80 g, 0.02 mol) and thionyl chloride (10 mL, 0.137 mol) were placed in the flask and refluxed for 10 h. During this period all the coumalic acid dissolved. The excess thionyl chloride was vacuum distilled using a water aspirator. The remaining oily material crystallized in the refrigerator.

The coumaloyl chloride obtained this way was used in preparation of benzyl coumalate with no further purification: IR 1750 cm^{-1} (C=O stretch); NMR ($CDCl_3$) δ 6.50 (1 H, dd, $J_{3,4}$ = 10, $J_{3,6}$ = 1 Hz), 7.90 (1 H, dd, $J_{4,3}$ = 10, $J_{4,6}$ = 3 Hz), 8.80 (1 H, dd, $J_{4,6}$ = 3, $J_{3,6}$ = 1 Hz).

Irradiation of Coumalic Acid in Methanol. A solution of coumalic acid (400 mg in 80 mL of methanol) (3.58×10^{-2} M) was introduced into ten 8 × 13 mm borosilicate culture tubes and irradiated (method 2) for 24 h at $h\nu > 310$ nm. The original colorless solution changed to light yellow at the end of the irradiation period. The solutions were combined and concentrated to 20 mL using a rotary evaporator and extracted with 200 mL of pentane using a continuous extractor, and the pentane solution was evaporated to yield 144 mg (36.20% total conversion) of a light yellow oil. When analyzed by gas–liquid chromatography (6 ft × 0.125 in. UCON Hp 10% on Chromosorb P 60/90) the oil contained four major compounds with retention times of 1.60, 3.24, 6.40, and 4.4 min in ratio of 3.2:5.2:4:1, respectively. These compounds were separated by preparative GLC (8 ft × 0.25 in. UCON LB 10% on Chromosorb P 60/80) and were identified to be methyl 5-methoxy-2,4-*trans*,*trans*-pentadienoate (**17**), methyl 5,5-dimethoxy-*cis*-2-pentenoate (**18**), methyl 5,5-dimethoxy-*trans*-2,2-pentenoate (**19**), and methyl coumalate (**12a**).

The infrared spectrum of **17** contained absorption bands at 1735 (C=O stretch), 1700, 1278 (=$COCH_3$ symmetrical and asymmetrical stretch), 1238, 1175, 1167 (C–O–C symmetrical and asymmetrical stretch), and 975 cm^{-1} (for all trans C=C conjugated); UV λ_{max} (CH_3OH) 284 nm (ε 19 500); mass spectrum *m/e* (rel intensity) 142 (3), 111 (100), 96 (58), 68 (62), and 59 (92).

The infrared spectrum of **18** on KBr showed the following bands: 1720 (conjugated C=O stretch), 1625 (C=C stretch), 1719, 1710, 1120 (C–O–C stretch known as acetal bands), 1070 (C–O–C symmetrical stretch), and 820 cm^{-1} (C=CH out of plane bend); UV λ_{max} (CH_3OH) 218 nm (ε 5000). The mass spectrum indicated no parent peak but a base peak was at *m/e* 111. Other peaks *m/e* (rel intensity) 143 (10), 142 (26), 112 (10), 75 (55), and 68 (95); NMR ($CDCl_3$) δ 3.05 (2 H, d of t), 3.39 (6 H, s), 3.75 (3 H, s), 4.35 (1 H, t), and 6.10 (2 H, m).

Compound **19** had a similar IR to that of **18**. Of special interest is the band at 974 cm^{-1} present in **19** which is assigned to out of plane bending vibrations in trans-disubstituted olefins. This band is absent in compound **18**. Other absorption frequencies were at 1720 (conjugated C=O stretch), 1650 (C=C stretch), 1205, 1172, 1128 (C–O–C, stretch known as acetal bands), 1275 (C–O–C asymmetrical stretch), and 1070 cm^{-1} (C–O–C symmetrical stretch); UV λ_{max} (CH_3OH) 218 nm (ε 15 500). The mass spectrum had a small peak at *m/e* 173, a base peak at *m/e* 75, and other significant fragments *m/e* (rel intensity) 143 (10), 112 (3), 111 (42), and 59 (25), NMR ($CDCl_3$) δ 2.57 (2 H, dd, J = 6 Hz), 3.39 (6 H, s), 3.78 (3 H, s), 3.52 (1 H, t, J = 6 Hz), 5.97 (1 H, t, d, $J_{1,3}$ = 16, $J_{1,3}$ = 1 Hz), and ~7 (1 H, m).

Irradiation of Isopropyl Coumalate in Methanol. A solution of isopropyl coumalate (1.50 g, 8.29×10^{-3} mol) in 370 ml of methanol was irradiated (method 1) for 7.5 h at 310 nm and 5 °C. At the end of this period the solvent was evaporated on a rotary evaporator and a TLC (silica gel PF-254, eluted with ether) of the resultant yellow oil obtained. Three compounds with R_f values of 0.60, 0.40, and 0.23 were present. The compound with R_f 0.60 was isopropyl coumalate and the compound with R_f 0.40 was the corresponding photolactone **13b**. The compound with R_f 0.25 was isolated by preparative TLC to yield 30 mg of a yellow oil: NMR ($CDCl_3$) δ 1.30 (12 H, 3, J = 6 Hz), 4.12 (3 H, s), 5.23 (1 H, quint, J = 6 Hz), 6.22 (1 H, d, $J_{2,3}$ = 16 Hz), 7.00 (1 H, s), 7.30 (1 H, d, $J_{3,2}$ = 16 Hz), 9.00 (1 H, broad). The mass spectrum of this compound had a molecular ion at *m/e* 214 (63) and two equally intense base peaks *m/e* 155 and 126. Other peaks were at *m/e* 154 (78), 140 (88), 123 (60), 112 (90), and 84 (61). On the basis of the above spectral data, structure **14b** was assigned to this compound.

Methyl coumalate behaved similarly and produced **14a** in small yield.

Methanolysis of 5-Carbomethoxy-3-oxabicyclo[2.2.0]hex-5-en-2-one (13a). A solution containing methyl coumalate (400 mg,

2.6×10^{-3} mol) in 35 mL of ahydrous ether was irradiated (method 2) for a period of 68 h. Immediately after irradiation a small amount of this solution was dissolved in 3.00 mL of methanol (2.77×10^{-4} M) and the UV spectrum recorded at time intervals of 0, 25, 50, 75, and 470 min. The ether was then evaporated on a rotary evaporator and 5.0 mL of methanol added to the entire sample. The reaction mixture was allowed to stand overnight. The methanol was evaporated and the NMR spectrum of the resultant yellow oil determined in $CDCl_3$. Only 30% of the photopyrone had reacted with the methanol but 70% had thermolyzed to methyl coumalate. The spectrum, in addition to the signals of methyl coumalate, contained the following signals: δ 3.78 (3 H, s), 3.98 (3 H, s), 6.33 (1 H, dd, $J_{2,3} = 16$, $J_{2,5} = 1$ Hz), 7.18 (1 H, m), and 7.38 ppm (1 H, dd), $J_{3,2} = 16$, $J_{3,5} = 2$ Hz) consistent with structure assigned to 4-carbomethoxy-5-methoxy-2,4-(*E*,*E*)-pentadienoic acid (**14a**).

Irradiation of Methyl Coumalate in Diethyl Ether. Preparation of 5-Carbomethoxy-3-oxabicyclo[2.2.0]hex-5-en-2-one (13a). A solution of methyl coumalate (500 mg, 3.25×10^{-3} mol) in 40 mL of anhydrous ether was irradiated (method 2) for a period of 68 h. At the end of this period the solvent was removed (rotary evaporator) and the resultant light yellow oil (485 mg) was molecularly distilled at 40 °C (0.005 Torr). Analysis of this oil proved it to be 5-carbomethoxy-3-oxabicyclo[2.2.0]hex-5-en-2-one (**13a**): IR (KBr) 1745 and 1840 cm^{-1}; UV λ_{max} (ether) 246 nm (ϵ 6550), 270 (shoulder) (3800); NMR ($CDCl_3$) δ 3.90 (3 H, s), 4.58 (1 H, m), 5.63 (1 H, dd, $J_{1,4} = 2$, $J_{1,6} = 4$ Hz), and 7.41 (1 H, dd, $J_{4,6} = 1$, $J_{3,4} = 4.5$ Hz); mass spectrum of **13a** *m/e* (rel intensity) 154 (20), 110 (100), 93 (44), 82 (90), 53 (60), and 39 (90). Other coumalate esters gave similar results when irradiated under similar conditions.

Irradiation of Methyl Coumalate in Benzene. A solution of 100 mg (6.50×10^{-4} mol) of methyl coumalate in 80 mL of anhydrous benzene (0.081 M) was irradiated (method 2) for 40 h. The solvent was evaporated and the infrared spectrum (neat on KBr plates) recorded. It contained the typical photopyrone carbonyl absorption band at 1825 cm^{-1} in addition to the methyl coumalate band at 1740 cm^{-1}. The NMR taken in $CDCl_3$ revealed that over 90% of methyl coumalate had been converted to the photopyrone **13a**. A small amount (<10%) of dimeric products was also present but these were not investigated. The bicyclic lactone **13a** was redissolved in benzene and allowed to stand on a lab bench at room temperature for over 1 week. At the end of this period the infrared spectrum was taken again though no significant change in the intensity of 1825 and 1740 cm^{-1} was observed. Isopropyl and benzyl coumalate also behaved similarly when irradiated in benzene.

Irradiation of Methyl Coumalate in Ether Sensitized with Benzophenone. In two 8 × 13 mm culture tubes was placed 16 mL of an ether solution containing methyl coumalate (200 mg, 1.29×10^{-3} mol). Benzophenone (0.50 mL, 9.9×10^{-2} M) in ether was introduced. The tubes were placed in a Rayonet reactor and irradiated at 5 °C (method 3) at 350 nm for 10.5 h.

At the end of this period, the reaction mixture remained colorless, but a white solid material had formed on the wall of the reaction vessel. The solid material was isolated by suction filtration, and washed with acetone. A white material (26 mg) which decomposed at 188 °C was isolated. This compound was later identified to be a [4 + 2] dimer adduct of methyl coumalate (**20**).

The filtrate was then concentrated to 8 mL and cooled in an ice bath. Another white solid crystallized out of solution. This compound was also isolated and washed with cold ether to yield 26 mg of white solid material which decomposed at 153–155 °C. This compound upon further analysis proved to be another [4 + 2] dimeric adduct of methyl coumalate (**21**).

The infrared spectrum of adduct **20** showed absorptions at 1780 (C=O stretch, lactone), 1725 (=C-C=O stretch, ester), 1675 (R_1R_2C=CR_3H stretch), 1265 [=C-C(=O)-O-C symmetrical stretch], and 770 cm^{-1} (R_1R_2C=CR_3H bend); NMR (Me_2SO-d_6) δ 3.65 (1 H, m), 3.79 (6 H, s), 3.95 (1 H, m), 4.00 (1 H, dd, $J_{7,12} = 6$, $J_{7,8} = 2$ Hz), 5.95 (1 H, m), 7.50 (1 H, dd, $J_{8,12} = 6$, $J_{1,12} = 2$ Hz), and 7.78 (1 H, s), mass spectrum *m/e* (rel intensity) 252 (44), 221 (100), 193 (45), 126 (22), 97 (43), 95 (43), 85 (40), 83 (43), and 69 (51). Anal. Calcd for $C_{14}H_4O_8$: C, 64.54; H, 3.89. Found: C, 64.51; H, 4.00.

The infrared spectrum of adduct **21** consisted of the following bands: 1700 (C=O stretch, ester), 1725 (C=O stretch, lactone), 1645 (R_1R_2C-CR_2H stretch), 1245 [=C-C(=O)-O-C asymmetrical stretch], 1175 [=C-C(=O)-O-C symmetrical stretch] 755 cm^{-1} (=C-H bend); NMR (Me_2SO-d_6) δ 3.72 (3 H, s), 3.74 (3 H, s), 4.20 (1 H, d, $J_{8,12} = 6$ Hz), 5.40 (1 H, d, $J = 2$ Hz), 5.69 (1 H, m), 6.20 (1 H, d, $J_{5,6} = 10$ Hz), 7.00 (1 H, d, $J_{6,5} = 10$ Hz), and 7.50 (1 H, dd, $J_{8,12} = 6$, $J_{1,12} = 2$ Hz); mass spectrum *m/e* (rel intensity) 264 (12), 252 (24), 221 (100), 193 (30), 163 (22), 154 (20.2), 126 (39), 95 (30), 85 (20), and 83 (20). Anal. Calcd for $C_{14}H_4O_8$: C, 54.54; H, 3.89. Found: C, 53.95; H, 4.19.

Irradiation of Methyl Coumalate in Ethyl Bromide. In a Pyrex test tube containing 8 mL of ethyl bromide was placed methyl coumalate (100 mg, 1.29×10^{-3} mol). Irradiation (method 2) was carried out at 5 °C for a period of 20 h. At the end of this period the solvent was evaporated and the solid material remaining dissolved in Me_2SO-d_6 for NMR analysis. Almost no methyl coumalate was present and the spectrum was identical with that of a mixture of **20** and **21**.

Irradiation of KBr Matrix at 254 nm. Control Experiment. A sample of 500 mg of anhydrous potassium bromide was made into a KBr pellet (method 4) and irradiated in a Rayonet photochemical reactor at 254 nm. The irradiation was monitored (infrared) and spectra were taken after 0, 2, 3, 4, 7, and 14.5 h of irradiation. From the obtained spectra the absorbance of the CO_2 band at 2330 cm^{-1} was measured and shown to be negligible over the first 7 h and to have reached a reading of 0.03 absorbance units in a 14.5-h period.

A. Irradiation at 254 nm. A potassium bromide disk was prepared by pressing a mixture of methyl coumalate (0.44 mg, 3.24×10^{-6} mol) in 370 mg of KBr in the usual manner. The infrared spectrum was recorded and the pellet irradiated (method 4) at 254 nm. The infrared spectrum was recorded again after 15, 30, and 60 min of irradiation. From the recorded IR spectra the absorbance of 1721 (C=O stretch, lactone), 1750 (C=O stretch, ester), and 2330 cm^{-1} (CO_2) were measured. The results are shown in order of increasing time of irradiation: 1721 cm^{-1}, 1.18, 0.87, 0.76, and 0.64; 1750 cm^{-1}, 1.25, 0.90, 0.15, and 0.34; 2330 cm^{-1}, 0, 0.18, 0.23, and 0.36.

B. Irradiation at 300 nm. A KBr matrix containing methyl coumalate (0.27 mg, 1.75×10^{-6} mol) and 489 mg of potassium bromide was prepared. The infrared spectrum was recorded and the pellet was irradiated (method 4) at 300 nm and 5 °C. The IR spectrum was obtained again after 15, 30, and 60 min of irradiation. A visual change from transparent to translucent, and from colorless to a light yellow, was observed. The absorbance at 1721, 1750, and 2330 cm^{-1} bands are shown in the order recorded: 1721 cm^{-1}, 1.05, 0.78, 0.65, and 0.53; 1750 cm^{-1}, 1.35, 1.00, 0.90, and 0.74; 2330 cm^{-1}, 0, 0.07, 0.16, and 0.31.

C. Irradiation at 350 nm. Methyl coumalate (0.13 mg, 8.45×10^{-7} mol) was mixed with 496 mg of KBr and pressed into a disk. The infrared spectrum was recorded and the matrix was irradiated (method 4) at 350 nm and 5 °C. The infrared spectrum was recorded after 10, 20, 30, and 40 min of irradiation. When the irradiation was over the visual properties of the matrix had not changed much. The absorbances of 1721, 1750, and 2330 cm^{-1} were measured and corrected for baseline. The result is shown in order of increasing time of irradiation: 1721 cm^{-1}, 0.64, 0.59, 0.57, 0.53, and 0.49; 1750 cm^{-1}, 0.48, 0.45, 0.41, 0.38, and 0.34; 2330 cm^{-1}, 0.00, 0.00, 0.00, 0.00 and 0.005.

D. Irradiation at 250 nm Followed by Irradiation at 300 nm. A KBr matrix containing 0.30 mg (1.94×10^{-6} mol) of methyl coumalate and 498 mg (4.19×10^{-3} mol) of KBr was prepared and after the IR spectrum was recorded it was irradiated (method 4) at 350 nm for 40 min. During this period the irradiation was interrupted after 10, 20, 30, and 40 min to record the infrared spectrum. The matrix was then irradiated for an additional 40 min at 300 nm and the IR spectra were recorded in the same manner. The visual appearance of the matrix did not change during the initial 40 min of irradition but the change (to yellow and translucent) was appreciable during the latter 40 min. The absorbance of 1550 (C=C stretch) and 2330 cm^{-1} (CO_2) bands after correction for baseline are presented in the order of the increasing time of irradiation at 350 and 300 nm: $h\nu$ 350, 1550 cm^{-1}, 0.120, 0.165, 0.115, 0.105, 0.100, and 0.091; 2330 cm^{-1}, 0, 0.0, 0.005, 0.01, 0.010, and 0.012; $h\nu$ 300, 1550 cm^{-1}, 0.091, 0.080, 0.075, 0.067, and 0.060; 2330 cm^{-1}, 0.012, 0.078, 0.130, 0.20, and 0.260.

In a subsequent experiment 7.12 mg (4.62×10^{-5} mol) of methyl coumalate was mixed with 4.46 g of anhydrous potassium bromide and made into nine KBr disks. The KBr disks were irradiated (method 4) at 350 nm for 7.6 h. The temperature was kept at 5 °C during the illumination time. The pellets were then pulverized (Wig-L-Bug) and dissolved in 25-mL of water. The aqueous solution was extracted with three 5-mL portions of methylene chloride. The methylene chloride extracts were combined, dried over anhydrous calcium chloride, and filtered, and solvent was evaporated to yield 5.0 mg of a light yellow, viscous material (70% recovery). When analyzed by HPLC (10 ft × 0.25 in. silica gel, $CHCl_3$, 1 mL/min) it contained nine compounds among which dimeric adducts **20** and **21** were identified by HPLC.

Isopropyl coumalate as well as benzyl coumalate, though not reported, behaved similarly when irradiated in a KBr matrix; the latter produced a trace amount of benzaldehyde also.

Acknowledgment. The work reported has been supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We gratefully acknowledge the generosity of the donors of this fund.

Registry No.—**12,** 500-05-0; **12a,** 6018-41-3; **12b,** 61752-09-8; **12c,** 61752-10-1; **13a,** 61752-11-2; **13b,** 61752-12-3; **13c,** 61752-13-4; **14a,** 61752-14-5; **14b,** 61752-15-6; **17,** 61752-16-7; 18, 61752-17-8; **19,** 61752-18-9; **20,** 61787-98-2; **21,** 61752-19-0; coumaloyl chloride, 23090-18-8.

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Photochemistry of 3-Ethoxy-3-methylpent-4-en-2-one, an α-Alkoxy β,γ-Unsaturated Ketone

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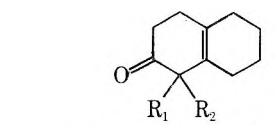
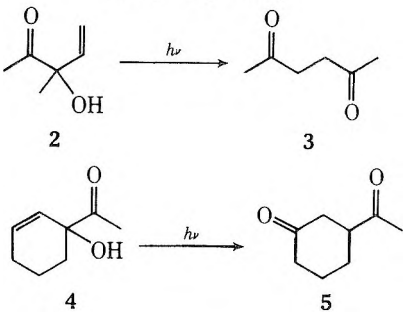
Irradiation of 3-ethoxy-3-methylpent-4-en-2-one gives (*E*)- and (*Z*)-5-ethoxyhex-4-en-2-one by 1,3-acyl shift; acetaldehyde, 3-methylpent-4-en-2-one, (*Z*)- and (*E*)-3-methylpent-3-en-2-one by Norrish type II cleavage; 2,3,4-trimethyl-2-vinyloxetan-3-ol (two isomers) by type II cyclization; and 3,4-dimethylhexane-2,5-dione (*dl*- and *meso*-) and 5-ethoxyhex-5-en-2-one by secondary reactions. Disappearance of 3-ethoxy-3-methylpent-4-en-2-one is neither sensitized by xanthone nor quenched by piperylene. The 1,3 shift is reversible. Mechanisms and relevance to other α-substituted β,γ-unsaturated ketones are discussed; isolation of γ-keto enol ethers from photolysis of α-ethoxy β,γ-unsaturated ketones provides circumstantial evidence that a γ-keto enol is the likely intermediate in photochemical conversion of α-hydroxy β,γ-unsaturated ketones to 1,4-diketones.

It has recently become apparent that α-substitution can cause dramatic alterations in the photochemical behavior of β,γ-unsaturated ketones.[1] For example, Engel et al.[2] have shown that α-methylation of **1a** enhances the likelihood of 1,3-shift (α-cleavage) at the expense of 1,2-shift products, although the multiplicity of the reactive excited state is uncertain.[3] Sasaki,[4] Carlson,[5] McMurry,[6] and we[7,8] have shown that α-hydroxylation introduces a synthetically useful modification to the usual reaction pattern of 1,3-acyl shifts. We previously reported the photochemistry of the two α-hydroxy β,γ-unsaturated ketones **2** and **4** which, on direct irradiation or with triplet sensitization, gave the 1,4-diketones **3** and **5**.[7,8] The rearrangements of **2** and **4** were suggested to involve a 1,3-acyl shift (probably via discrete acetyl and allyl radicals), followed by tautomerization of the resultant γ-keto enol. The (inefficient) sensitized 1,3-acyl shift of both **2** and **4**, though not unprecedented,[9] is highly unusual in β,γ-unsaturated ketone photochemistry.



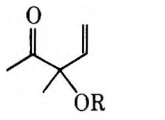
1a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = CH_3$



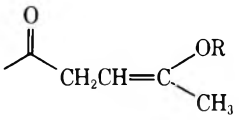
2 **3**

4 **5**

This report describes the photochemistry of a related molecule, 3-ethoxy-3-methylpent-4-en-2-one (**6a**), whose excited state reactivity is unusually complex and substantially different from that of the hydroxy analogue **2**.[10] The reasons for extending our study of α-hydroxy substituted β,γ-unsaturated ketones to α-alkoxy analogues (**6b**) were several. First,



6a, R = CH_2CH_3
b, R = alkyl



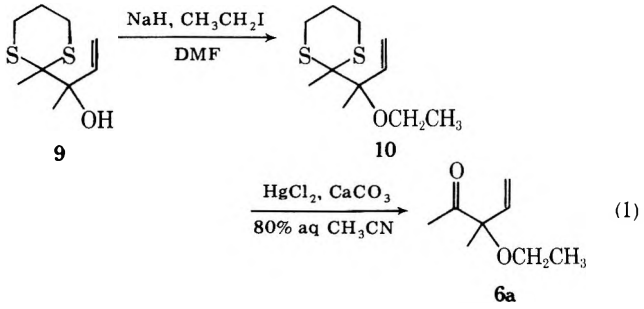
7, R = H
8, R = alkyl

it is possible to write alternative mechanisms for the **2** → **3** and **4** → **5** transformations. For example, although the 1,3-acyl shift/enol ketonization mechanism for the photorearrangement of **2** is well precedented,[1] the intermediacy of enol **7** was not proven by physical detection. An α-alkoxy analogue such as **6b** could provide circumstantial evidence for the validity of the **2** → **7** → **3** mechanism since an analogous 1,3-acyl shift in **6b** should halt at the stage of an (isolable) enol ether **8**. A complication attending this idea is the γ hydrogens available in all but tertiary alkoxy substituents, which would be susceptible to competing Norrish type II reactions. However, assessing the competition between the 1,3 shift and γ-H abstraction was also of fundamental interest.[11]

From a synthetic point of view, were the **6b** → **8** transformation to proceed in reasonable yield, it would provide a useful synthetic route to γ-keto enol ethers. Such half-protected 1,4-diketones would have considerable utility as synthetic intermediates.

Results

Synthesis. The synthesis of 3-ethoxy-3-methylpent-4-en-2-one (**6a**) was accomplished using three different synthetic schemes, the most efficacious of which is summarized in eq 1. The dithiane **9** was available from an intermediate step in the synthesis of **2**.[7,12,13] Addition of sodium hydride to a solution of the dithioketal **9** and ethyl iodide in dry dimethylformamide at 0 °C gave 92% of the ether **10**. Mercuric chloride cleavage[12] of the dithiane **10** afforded the desired ether (**6a**) in 33% yield after careful purification by distillation and preparative gas chromatography.



(1)

Direct alkylation of **2** afforded **6a** in modest yield, but the anticipated α-alkylation side products diminished the yield substantially. Synthesis of **6a** from **2** by successive ketalization, ether oxygen alkylation, and acid-catalyzed cleavage of the ketal in acetone was successful, but the more direct approach shown in eq 1 gave better overall yields. The structural assignment for **6a** was supported by its UV, NMR, and mass spectra (cf. Experimental Section).

Direct Irradiation. To avoid photoproduct hydrolysis (symptoms: ethanol and 2,5-hexanedione as products, variable product yields) during irradiation and GLC analysis, several precautions were necessary: (1) ethoxide-washed and oven-dried photolysis and collection tubes; (2) sample preparation in a drybox; (3) scrupulously and freshly dried solvents; (4) double septums over and molecular sieves in photolysis tubes; and (5) glass GLC columns and a high-pH support (Chromosorb G-NAW). Carbon disulfide and sodium-dried benzene-d_6 were used rather than chlorocarbons for IR and NMR spectra of the most moisture-sensitive samples.

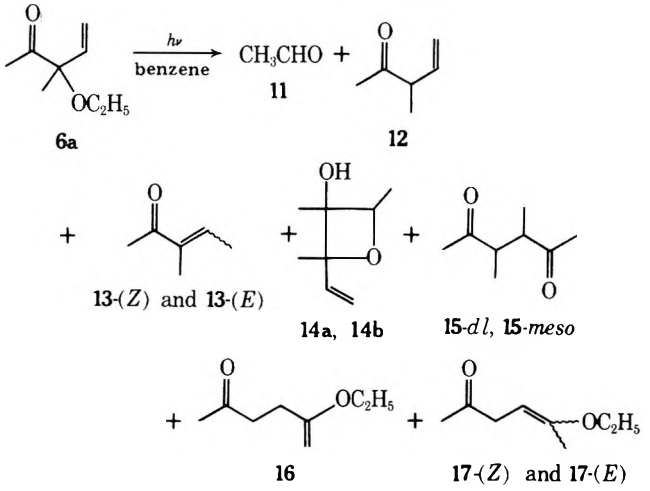
Table I. Photoproducts from Irradiations of 3-Ethoxy-3-methylpent-4-en-2-one

Compd	Retention time, min[a]	Yield, %[b] direct	Yield, %,[b,c] with piperylene
11	2.6	4	4
12	9.1	2	7
13-(*Z*)	12.4	4	7
13-(*E*)	16.2	5	9
14a[d]	28.6	6	7
14b[d]	35.4	3	3
15a[e]	47.9	2	0
15b[e]	55.7	2	0
16	58.1	3	5
17a[f]	71.2	2	4
17b[f]	76.1	3	5

[a] On a 20 ft × 9 mm o.d. glass column of 5% SE-30 on 60/80 Chromosorb G-NAW at 85 °C, 95 mL/min. [b] Uncorrected for detector response. [c] 0.3 M piperylene and 0.3 M **6** in benzene. [d] One of four possible stereoisomers, absolute stereochemistry undetermined. [e] *dl* and meso stereoisomers; correspondence to individual GLC fractions undetermined. [f] *E* and *Z* isomers; absolute stereochemistry not unambiguously determined.

When samples of **6a** (0.2 M in benzene, *tert*-butylbenzene as standard) were prepared, irradiated, and analyzed with the precautions indicated, the GLC trace revealed (after 2 h of irradiation) that 11 principal photoproducts[14] and numerous trace products were formed (Scheme I). The hydrolysis products, ethanol and 2,5-hexanedione (**3**), were not observed under rigorously dry and acid-free conditions.

Scheme I. Direct Photolysis of 3-Ethoxy-3-methylpent-4-en-2-one



The 11 principal photoproducts were isolated by preparative GLC (cf. Table I for yields and retention times). Comparison of IR and NMR spectra with published ones identified acetaldehyde (**11**), 3-methylpent-4-en-2-one (**12**),[15] and (*Z*)- and (*E*)-3-methylpent-3-en-2-one [**13**-(*Z*), **13**-(*E*)].[15-18] The next two fractions were identified as two of the four possible racemic stereoisomers of 2,3,4-trimethyl-2-vinyloxetan-3-ol (**14a, 14b**) based on NMR (two methyl singlets, methyl doublet, methine quartet, vinyl ABX), IR (hydroxyl, vinyl, and oxetane bands), and mass spectra (cf. Experimental Section).

The *dl* and meso modifications of 3,4-dimethylhexane-2,5-dione (**15a,b**) were identified by comparison of IR, NMR, and mass spectra[19] and GLC retention times to those of the authentic materials prepared as a *dl*–meso mixture from 2-butanone and lead dioxide according to Wolf.[20]

Three enol ethers were identified on the basis of IR, NMR, and mass spectra, and by their particular susceptibility to hydrolysis to 2,5-hexanedione and ethanol. 5-Ethoxyhex-5-en-2-one (**16**) was distinguished from the others by the terminal methylene–enol ether moiety (NMR δ 3.83 and 3.91 doublets; IR 975 and 795 cm^{-1}). Two GLC fractions (**17a, 17b**) were identified from IR, NMR, and mass spectra as 5-ethoxyhex-4-en-2-one. Both had enol ether IR bands (in CS_2: **17a**, 790 cm^{-1}; **17b**, 810 cm^{-1}) and, in the NMR (C_6D_6), 1-H vinyl triplets (**17a**, δ 4.70; **17b**, δ 4.57) coupled (J = 7 Hz) to a methylene doublet (**17a**, δ 3.11; **17b**, δ 2.77). More fine spin–spin splitting between methylene, vinyl H, and vinyl methyl could be seen in **17a**. Since 17-(*Z*) should be expected to have the more shielded vinyl hydrogen, less shielded vinyl methyl, and the larger allylic coupling,[21-23] the NMR contradictions precluded unambiguous distinction as to which fraction of **17a,b** was 17-(*E*) and which was 17-(*Z*).

Plots of product yields vs. irradiation time showed clear induction periods for the 3,4-dimethylhexane-2,5-diones **15**, indicating that they were secondary photoproducts. The plot for **16** was ambiguous. No induction periods were seen in formation of photoproducts **11, 12, 13, 14,** and **17.**

In addition to the identified photoproducts, ca. 25 additional trace products could be seen in the GLC trace when the temperature was programmed to 200 °C. Quantification and identification were not feasible.

Photolyses of 3-Ethoxy-3-methylpent-4-en-2-one with Added Sensitizers or Quenchers. Two solutions of 0.3 M 3-ethoxy-3-methylpent-4-en-2-one (**6a**) in dry benzene with *tert*-butylbenzene as standard, with 0.9 M piperylene added to one sample, were degassed and irradiated in parallel with a 450-W Hanovia medium-pressure mercury arc lamp for a total of 3 h. Aliquots were withdrawn at regular intervals for GLC analysis (5% SE-30, 85 °C, 95 mL/min). No quenching of the disappearance of **6a** could be observed.

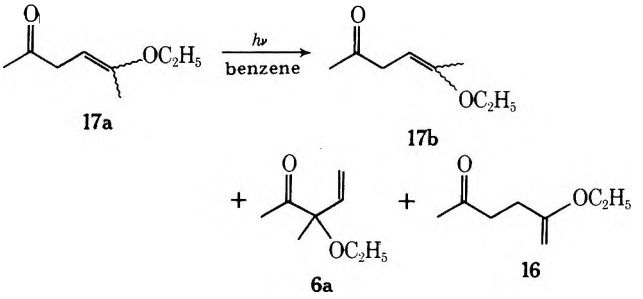
Although no change in the rate of keto ether loss was observed, many other differences were apparent in the GLC traces of the two photolysates. Most notable was the complete lack of either isomer of 3,4-dimethylhexane-2,5-dione (**15**) in the piperylene-quenched photolysis. Most other photoproducts appeared more rapidly and rose to a greater overall yield in the piperylene-quenched photolysis (cf. Table I).

Parallel photolyses were also run on two 0.5 M solutions of **6a** in benzene containing *tert*-butylbenzene standard, which were identical except that one was saturated with xanthone (0.19 M). A 6-h irradiation at 365 nm and a bandwidth of 23 nm, obtained with a 1000-W Osram super-pressure mercury arc lamp with a Schoeffel GM-250 grating monochromator (conditions under which the xanthone would absorb virtually 100% of the light), was monitored by GLC.

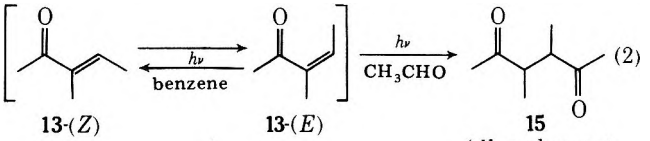
At the end of the irradiation no loss of **6a** could be observed in either photolysis. Using trans–cis piperylene isomerization (Φ = 0.44)[24-26] as actinometer, and assuming that no more than 5% of **6a** could have reacted without detection, an upper limit for the quantum yield for sensitized disappearance of **6a** would be 4×10^{-3}.

Direct Photolysis of 5-Ethoxyhex-4-en-2-one in Benzene. A sample of 5-ethoxyhex-4-en-2-one (**17a**), isolated by preparative GLC and dissolved to make a 1% solution in dry benzene-d_6 according to the precautions presented earlier (vide ante), was irradiated with a Corex D-filtered mercury arc lamp, and reaction was monitored by GLC. After 30 min three new GLC peaks were apparent, having identical retention times with **17b**, the other isomer of 5-ethoxyhex-4-en-2-one, 3-ethoxy-3-methylpent-4-en-2-one (**6a**), and 5-ethoxyhex-5-en-2-one (**16**) (Scheme II). The remaining photolysate was diluted and analyzed by FT NMR, which clearly showed that both isomers of **17** were present. No photoequilibrium could be established because of the gradual accumulation of secondary photoproducts. From the relative rates of production of **6a** and **17b**, it appears likely that the latter is a secondary photoproduct.

Scheme II. Photolysis of 5-Ethoxyhex-4-en-2-one in Benzene



Photolysis of (*E*)-3-Methylpent-3-en-2-one with Acetaldehyde in Benzene-d_6. A 1% solution of (*E*)-3-methylpent-3-en-2-one [13-(*E*)], with an eightfold excess of acetaldehyde, and *tert*-butylbenzene as standard, in sodium-dried benzene-d_6 was irradiated for 2.5 h with a Corex-filtered mercury arc lamp; progress of the reaction was followed by GLC. After 15 min of irradiation a GLC peak representing (*Z*)-3-methylpent-3-en-2-one [13-(*Z*)] was the only detectable photoproduct. Morrison and Rodriquez[27] have previously documented this example of photochemical cis–trans isomerization. The photolysis was continued for 150 min, at which time more than 95% of the (*E*)- and (*Z*)-3-methylpent-3-en-2-ones had disappeared and two new products had appeared, which were identified at *dl*- and *meso*-3,4-dimethylhexane-2,5-dione (**15a,b**) on the basis of GLC retention times (eq 2).



Discussion

Primary Photochemistry of 3-Ethoxy-3-methylpent-4-en-2-one. The photochemistry of the α-ethoxy β,γ-unsaturated ketone **6a** proved significantly more complicated than that of the α-hydroxy analogue **2**,[7] as the 11 principal photoproducts,[14] two hydrolysis products, and numerous trace products attest. However, all of the primary photoproducts can be accounted for in terms of competing 1,3-acyl shift (**11, 17a,b**) and Norrish type II [**11, 12, 13**-(*Z,E*), and **14a,b**] processes. The other products (**15a,b** and **16**) arise via secondary photochemical reactions (vide infra).

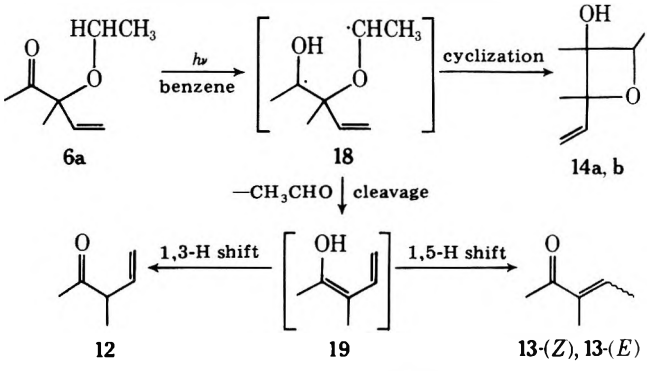
Both sets of primary photoreactions can be rationalized as originating in either the n–π^* singlet (S_1) or n–π^* triplet (T_2)[3] of **6a**. The α-ethoxy ketone **6a** showed a normal hypsochromic shift of the n–π^* absorption band in polar solvents [λ_{max} 297, 305, 315 (sh), and 325 nm (sh) in c-C_6H_{12}; 295 (sh), 302, 313 (sh), and 325 nm (sh) in acetonitrile]. The analogous α-hydroxy ketone **2** showed a *bathochromic* polar solvent shift of the long wavelength absorption band.[7] Comparison of the spectra of **2** and **6a** supports previous conclusions[4,7,28,29] that internal hydrogen bonding of α-hydroxy ketones in nonpolar solvents is the cause of their atypical bathochromic n–π^* polar solvent shifts.

The disappearance of **6a** could neither be sensitized with xanthone (E_T = 74 kcal mol^{-1}) nor quenched with piperylene. The absence of any discernible triplet-sensitized reactivity in **6a** (other than inefficient long-term decomposition) is probably attributable to an invisible free-rotor effect.[21] Since xanthone's triplet energy is probably too low to sensitize the T_2 of **6a**, these results are compatible with very fast reaction from either T_2 or S_1 on direct irradiation.

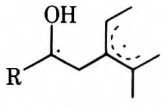
The 1,3-shift products, enol ethers **17**-(*Z*) and **17**-(*E*), are the analogues of the γ-keto enol **7**, which had been postulated as an undetected intermediate in the **2** → **3** rearrangement. Whether the 1,3 shift in **6a** is concerted or stepwise is hard to assess. Acetaldehyde (**11**) and traces of biacetyl were the only α-cleavage products detected, and most of the **11** more likely originates in Norrish type II cleavage as companion to the Δ^4- and Δ^3-3-methylpenten-2-ones **12** and **13**. In either case, isolation of enol ethers **17** from photolysis of the α-alkoxy ketone **6a** provides strong circumstantial evidence for intermediacy of enol **7** in the photolysis of the α-hydroxy analogue **2**. Tautomerization of **17** is blocked by the ether function, but diketone **3** is readily obtained by hydrolysis. The low yields of enol ethers **17** obviate any synthetic utility in this system as a half-protected 1,4-diketone.

The origins of acetaldehyde (**11**), unsaturated ketones **12**, **13**-(*E*), and **13**-(*Z*), and oxetanol isomers **14a,b** are in Norrish type II pathways (Scheme III) which compete with the 1,3-acyl shift. γ-Hydrogen abstraction can be followed by cyclization of the biradical **18** to give the oxetanols (**14**) or by cleavage to give acetaldehyde and the transient enol **19**. Tautomerization of the enol by 1,3- and 1,5-hydrogen shifts leads to **12** and **13**, respectively.

Scheme III. Norrish Type II Reactions of 3-Ethoxy-3-methylpent-4-en-2-one



There are many examples of type II reactions in β,γ-unsaturated ketones which have involved hydrogen abstraction from a β-alkyl group to give a diradical of type **20** and subsequent cyclization rather than cleavage.[1,9,11] Wagner has explained the absence of type II elimination as a result of the orthogonality of the allylic π radical to the C_2–C_3 bond.[30] This rationale does not apply to **6a**, in which H abstraction is from a β′-alkyl group to give the quite different diradical **18** (Scheme III).

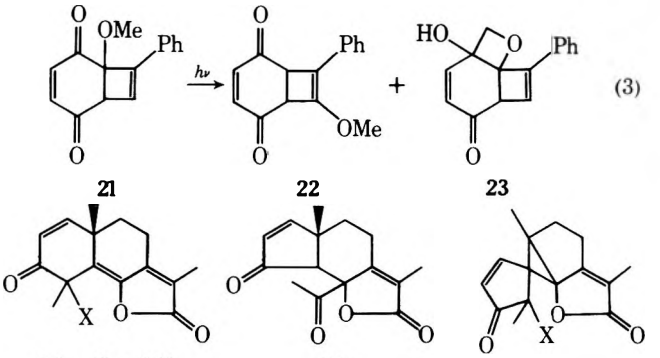


20

The photochemistry of **6a** more closely resembles results of Yates and Szabo,[31] LaCount and Griffin,[32] and Lewis and Turro[33] for various α-alkoxy ketones and acetophenones, in which both type II cleavage and cyclization occur competitively.

It is difficult to gauge precisely the partitioning of **6a** between the several available pathways because of the number of minor, unidentified products. However, that the n–π* singlet of **6a** is partitioned between 1,3 shift and γ-H abstraction, whereas the photochemistry of the hydroxy analogue **2** was uncomplicated by type II reactions, demonstrates the significant γ-hydrogen substituent effect. Dramatic enhancement of γ-H abstraction by adjacent alkoxy functionality has been demonstrated previously by several groups,[33–35] and quantified and explained by Wagner.[34] In **6a**, the best estimates of the proportioning are the product yields in runs with added piperylene which was shown not to quench disappearance of **6a** or appearance of any primary photoproducts, but which did quench secondary triplet decompositions of the primary products. Under these conditions the yield ratio (**12** + **13** + **14**):(**17**) gauges the γ-H abstraction:1,3-shift partitioning as ca. 4:1 (a typical value[33–35]). Similarly, the (**12** + **13**):(**14**) ratio measures the type II cleavage:cyclization ratio as ca. 2:1 (cf. Table I). These values, of course, measure only products, not reactivities, since reversion to **6a** from reaction intermediates has not been measured.

Few closely related systems have been studied.[1] Anet and Mullis[36] did report the photochemistry of the α-methoxy β,γ-unsaturated ketone **21**, which partitioned about 3:1 between 1,3 shift (**22**) and type II cyclization (**23**), with no type II cleavage and apparently no 1,3 shift reversal (eq 3). McMurry[37] has recently reported the photochemistry of 4-hydroxy- (**24a**)[6] and 4-acetoxysantonene (**24b**).[37] Hydroxy ketone **24a** gives the *A*-nor-6-acetyl compound **25** (by 1,2 shift and cyclopropanol rearrangement) as the major direct and sole triplet-sensitized product. In contrast to **24a** and **6a**, the α-acetoxy β,γ-unsaturated ketone **24b** gives decarboxylation product **24c** and double bond migration isomers in the triplet state, and enone-type rearrangements to **26** in the singlet.[37] The sensitized photolyses of the 1,2-dihydro analogues of **24a** and **24b** gave analogous triplet photochemistry, but the singlet photochemistry was not reported.[36,37] The diverging reactions of the α-oxy ketones such as **2**, **4**, **6a**, **24a**, and **24b** leave many unanswered questions about the role of α-alkoxy substituents in β,γ-unsaturated ketone photochemistry.

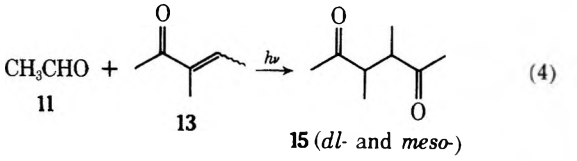


24a, X = OH
b, X = OAc
c, X = CH_3

25

26a, X = OAc
b, X = CH_3

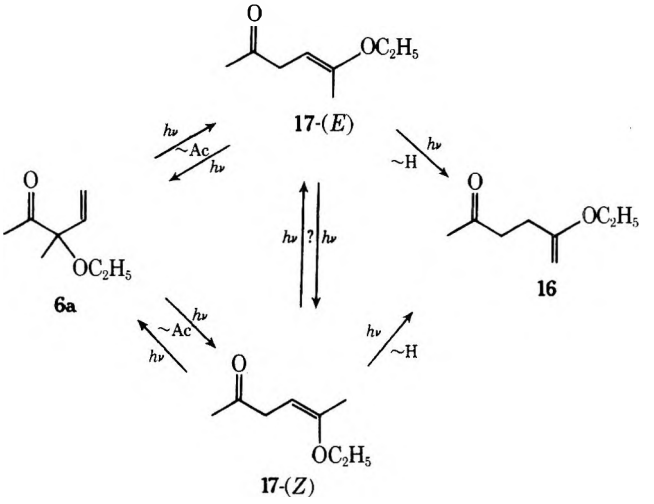
Secondary Photochemical Reactions. The *dl*- and *meso*-3,4-dimethylhexane-2,5-diones **15** were identified as secondary photoproducts from the observations that (a) buildup of diketones **15** shows an induction period, accelerating when photolysis of **6a** is about 30% complete; and (b) production of diketones **15** is totally quenched by 0.9 M piperylene (Table I), while disappearance of **6a** is not. The likely source of diketones **15** was shown by an independent photolysis to be photoaddition of acetaldehyde (**11**) to 3-methylpent-3-en-2-one (**13**) under the photolysis conditions for **6a** (eq 4). Fraser-Reid et al. have also recently reported photosynthesizing 1,4-diketones by photoaddition of aldehydes to enones[38] under conditions comparable to those employed here.



(4)

The origin of 5-ethoxyhex-5-en-2-one (**16**) can be traced to further rearrangement of the enol ethers **17**, as suggested by the rise in yield of **16** at the expense of **17** during photolysis of **6a**. Photolysis of isolated **17** gave **16** via a 1,3-H shift and **6a** via a 1,3-acyl shift (Scheme IV). Both are presumed singlet reaction products since their formation was not quenched by piperylene. In addition, **17** undergoes cis–trans isomerization under the photolysis conditions. Although olefin isomerization is often seen in unconstrained β,γ-unsaturated ketones as a triplet process,[1,21] the **17**-(*E*) ⇌ **17**-(*Z*) isomerization more likely results from sequential 1,3-acyl shifts, since **6a** appeared more rapidly than **17b** in photolyses of **17a**.

Scheme IV. Photochemistry of 5-Ethoxyhex-4-en-2-one



Although the secondary photochemistry of the other primary products was not explored, the oxetanols **14** appeared photolytically stable since their yields were not affected by added piperylene. The oxetanols also were stable to hydrolysis under normal conditions.

Experimental Section[39]

2-Methyl-2-(1-ethoxy-1-methylprop-2-en-1-yl)-1,3-dithiane. To an oven-dried 500-mL three-neck round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet, and dry addition funnel were added 200 mL of dimethylformamide, dried by distillation over calcium hydride, and 27.3 g (0.175 mol) of ethyl iodide. Sodium hydride (7.38 g of a 57% oil dispersion, 0.175 mol) was washed free of oil with pentane and added to the reaction flask all at once. 2-Methyl-2-(1-hydroxy-1-methylprop-2-en-1-yl)-1,3-dithiane[7] (20.4 g, 0.100 mol) dissolved in 80 mL of dry DMF was added with stirring to the reaction flask which was cooled in an ice bath. The reaction mixture was warmed and stirred at room temperature for 20 h. The reaction mixture was diluted with 330 mL of water and extracted with ether (5 × 100 mL), and the combined ether extracts were washed with 250 mL of brine. The ethereal solution was dried over anhydrous sodium sulfate and concentrated in vacuo to give 23.1 g of a pale yellow liquid. Simple distillation afforded 21.5 g (93%) of clear, colorless 2-methyl-2-(1-ethoxy-1-methylprop-2-en-1-yl)-1,3-dithiane: bp 107–108 °C (0.5 Torr); infrared (neat film) absorptions at 3089 (vinyl), 2985, 2932, 1440, 1410, 1385, 1365, 1275, 1240, 1111, 1074, 1038, 996 (vinyl), and 924 cm^{-1} (vinyl); NMR (CCl_4) resonances at δ 1.17 (3 H, triplet, J = 6.5 Hz, CH_3CH_2–), 1.40 (3 H, singlet, methyl), 1.47 (3 H, singlet, methyl), 1.67–2.20 (2 H, multiplet, C-5 methylene), 2.28–3.00 (4 H, multiplet, C-4 and C-6 methylenes), 3.33 (2 H, quartet, J = 6.5 Hz, CH_3CH_2–), 5.08, 5.22, and 6.24 (3 H, ABX pattern, cis terminal H, trans terminal H, and single vinyl H, respectively, J_{AX} = 17, J_{BX} = 11, J_{AB} = 2 Hz).

3-Ethoxy-3-methylpent-4-en-2-one. To a 2-L three-neck round-bottomed flask fitted with mechanical stirrer, 1-L addition funnel, condenser, and dry nitrogen inlet were added 900 mL of 80% aqueous acetonitrile, 53.2 g (0.196 mol) of mercuric chloride, and 22.2 g (0.222 mol) of calcium carbonate (to buffer the solution near pH 7). 2-Methyl-2-(1-ethoxy-1-methylprop-2-en-1-yl)-1,3-dithiane (20.7 g, 0.0891 mol) dissolved in 600 mL of 80% aqueous acetonitrile was added dropwise to the reaction mixture. After stirring at room temperature for 1 h, the reaction mixture was refluxed for an additional 16 h. A tan solid which began to form after 1 h was removed after reflux by suction filtration through a pad of Celite 512 (AW). The filter cake was washed thoroughly with ether. The combined filtrate and ether solutions were diluted with 1 L of additional ether and this solution was washed with 5 M ammonium acetate (2 × 600 mL). The organic layer was dried over anhydrous sodium sulfate and then concentrated to ca. 60 mL by distillation through a 4-ft vacuum-jacketed fractionating column of glass helices. Preparative GLC (6.5 ft × 0.75 in. 20% UC-W98 on 60/80 Chromosorb P-DMCS, 93 °C) followed by simple distillation afforded 4.1 g (33%) of clear, colorless 3-ethoxy-3-methylpent-4-en-2-one: bp 159–161 °C; infrared (CCl_4) absorptions at 3092 (vinyl), 2990, 2938, 2905, 2885, 1716 (carbonyl), 1628 (vinyl), 1438, 1403, 1390, 1350, 1190, 1124 (ether), 1065, and 928 cm^{-1} (vinyl); NMR (benzene-d_6) resonances at δ 1.17 (3 H, triplet, J = 7 Hz, CH_3CH_2–), 1.43 (3 H, singlet, α-methyl), 2.16 (3 H, singlet, acetyl methyl), 3.20 and 3.28 (2 H, overlapping quartets, J = 7 Hz, nonequivalent O-methylene hydrogens), 5.10, 5.37, and 5.88 (3 H, ABX pattern, cis vinyl H, trans vinyl H, single vinyl H, respectively, J_{AX} = 17, J_{BX} = 10, J_{AB} = 2.5 Hz); ultraviolet λ_{max} at 297 nm (ϵ 141), 305 (139), 315 (sh), and 325 (sh) in cyclohexane, λ_{max} at 295 nm (sh), 302 (ϵ 137), 313 (sh), 325 (sh) in acetonitrile; significant mass spectral fragmentations (with rel intensities) at m/e 142 (0.02, P), 99 (90), 78 (32), 71 (92), 43 (100), 41 (23), 39 (21), 29 (32), 27 (53), and 15 (42).

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

3,4-Dimethylhexane-2,5-dione. Using a procedure outlined by Wolf,[20] 60 g (0.83 mol) of 2-butanone and 20 g (0.083 mol) of lead dioxide were refluxed for 28 h in a 300-mL three-neck round-bottomed flask equipped with a condenser and dry nitrogen inlet. After ca. 3 h, the black solid had become yellow. The solid was removed by suction filtration upon completion of reflux. Distillation of the filtrate through a 10-cm Vigreux column gave a low-boiling fraction (bp <80 °C) and 3.88 g (33% based on PbO_2 used) of 3,4-dimethylhexane-2,5-dione, bp 85–95 °C (17–20 Torr), as a mixture of the *dl* and meso isomers. Separation of the isomers was accomplished by preparative GLC (20 ft × 9 mm o.d. glass, 4% SE-30 on 60/80 Chromosorb G-NAW, 85 °C): fraction 1 (retention time 41.3 min) had infrared (CCl_4) absorptions at 2985, 2947, 2890, 1710 (carbonyl), 1454, 1421, 1355, 1280, 1195, 1163, 1088, and 945 cm^{-1}; NMR (CCl_4) resonances at δ 1.02 (6 H, doublet, J = 6.5 Hz, 3,4-dimethyls), 2.10 (6 H, singlet, terminal methyls), and 2.40–3.00 (2 H, multiplet, methines); fraction 2 (retention time 48.2 min) had infrared (CCl_4) absorptions at 2985, 2948, 2890, 1710 (carbonyl), 1460, 1423, 1355, 1158, 1082, and 955 cm^{-1}; NMR identical with that of fraction 1. No attempt was made to identify which GLC fraction was the *dl* mixture and which was the meso component.

Direct Irradiation of 3-Ethoxy-3-methylpent-4-en-2-one. Photolysis samples were prepared in oven-dried, ethoxide-washed thin-walled Pyrex NMR tubes under a dry nitrogen atmosphere. In a typical experiment, 100 μL (0.0912 g, 0.642 mmol) of 3-ethoxy-3-methylpent-4-en-2-one, 6.0 μL of *tert*-butylbenzene as standard, 1.90 mL of sodium-dried spectrograde benzene, and ca. 25 Linde 4-A molecular sieves were added to the NMR tube. The photolysis tube was sealed by first wiring on one and then a second (larger) serum cap. Samples were degassed by three freeze–pump–thaw cycles at 10^{-4} Torr, and irradiated with a Corex-D filtered 450-W, medium pressure Hanovia mercury arc lamp for periods up to 6 h. Photolysis was followed by GLC analysis on a 20 ft × 9 mm o.d. glass column packed with either 4 or 5% SE-30 on 60/80 Chromosorb G-NAW. In analytical studies 100-μL aliquots were removed from the photolysis tube every 15 min; GLC analysis revealed the immediate buildup of 11 major[14] and many minor photoproducts with the concomitant loss of the 3-ethoxy-3-methylpent-4-en-2-one peak. Two peaks (corresponding to the 3,4-dimethylhexane-2,5-diones) appeared more slowly, but grew to be major photoproducts after ca. 1.5 h of irradiation. The major photoproducts were isolated by preparative GLC after irradiation periods of ca. 1.5 h, using oven-dried and base-washed collection devices. The principal photoproducts, in order of their GLC retention times, are listed below with their respective GLC elution times (20 ft × 9 mm o.d. glass 5% SE-30 on 60/80 Chromosorb G-NAW, 85 °C, 95 mL/min) and maximum percent yields.[14]

1. Acetaldehyde (2.6 min, yield 4%) was characterized by comparison of its GLC retention time, NMR, and IR spectra with those of authentic material.

2. 3-Methylpent-4-en-2-one (9.1 min, yield 2%) was characterized by comparison of its IR and NMR spectra to published data:[15] NMR (CCl_4) resonances at δ 1.16 (3 H, doublet, J = 7 Hz, C-3 methyl), 2.04 (3 H, singlet, acetyl methyl), 2.75–3.40 (1 H, five-peak multiplet with fine splitting, methine), and 4.65–6.0 (3 H, ABX pattern, vinyl H's) [lit.[15] NMR δ 1.19 (doublet, J = 6.9 Hz), 2.07 (singlet), 3.12 (pentet, J = 7 Hz), and 5–6 (multiplet)].

3. (*Z*)-3-Methylpent-3-en-2-one (12.4 min, yield 4%) was characterized by comparison of NMR and infrared spectra to spectra of authentic material.[15–18]

4. (*E*)-3-Methylpent-3-en-2-one (16.2 min, yield 5%) was characterized by comparison of NMR and infrared spectra to those of authentic material.[15–18]

5. 2,3,4-Trimethyl-2-vinyloxetan-3-ol A (28.6 min, yield 6%), one of four possible racemic stereoisomers, absolute stereochemistry undetermined, was characterized by its infrared, NMR, and mass spectra: infrared (CCl_4) absorptions at 3575 (hydroxyl), 3093 (vinyl), 2982, 2940, 2900, 1630 (vinyl), 1441, 1391, 1376, 1332, 1260 (oxetane), 1217, 1142, 1097, 1054, 987, 952 (oxetane), 940, and 886 cm^{-1}; NMR ($CDCl_3$) resonances at δ 1.18 (3 H, doublet, J = 7 Hz, C-4 methyl), 1.30 and 1.38 (3 H each, singlets, C-2 and C-3 methyls), 2.26 (1 H, singlet, hydroxy), 4.53 (1 H, quartet, J = 7 Hz, methine), 5.34, 5.53, and 5.91 (3 H, ABX pattern, cis terminal H, trans terminal H, single vinyl H, respectively, J_{AX} = 17, J_{BX} = 10, J_{AB} = 2.5 Hz).

Anal. Calcd for $C_8H_{14}O_2$: M^+· 142.0994. Found: 142.1016.

6. 2,3,4-Trimethyl-2-vinyloxetan-3-ol B (35.4 min, yield 3%), one of four possible racemic stereoisomers, absolute stereochemistry undetermined, was characterized by infrared, NMR, and mass spectra: infrared (CS_2) absorptions at 3620 (hydroxyl), 3110 (vinyl), 2980, 2930, 2915, 1370, 1325, 1260 (oxetane), 1230, 1185, 1065, 1100, 957 (oxetane), 890, and 860 cm^{-1}; NMR ($CDCl_3$) resonances at δ 1.24 (3 H, singlet, methyl), 1.27 (3 H, doublet, J = 6 Hz, C-4 methyl), 1.32 (3 H, singlet, methyl), 1.82 (1 H, singlet, hydroxy), 4.42 (1 H, quartet, J = 6 Hz, methine), 5.11, 5.31, and 5.91 (3 H, ABX pattern, cis terminal H, trans terminal H, single vinyl H, respectively, J_{AX} = 17, J_{BX} = 10, J_{AB} = 2 Hz); significant mass spectral fragmentations (with relative intensities) at m/e 124 (1, P − 18), 58 (22), 43 (100), and 15 (16).

7 and 8. 3,4-Dimethylhexane-2,5-dione was isolated as two GLC fractions corresponding to indistinguishable *dl* and meso modifications, identified by IR, NMR, and mass spectra[19] identical with those of authentic material prepared according to Wolf:[20] fraction 7 (47.9 min, yield 2%) and fraction 8 (55.7 min, yield 2%).

9. 5-Ethoxyhex-5-en-2-one (58.1 min, yield 3%) was characterized by infrared (CS_2) absorptions at 3120 (vinyl), 2980, 2925, 1725 (carbonyl), 1660 (vinyl), 1362, 1300, 1280, 1272, 1160, 1082, 975 (OCH=CH_2), and 795 cm^{-1} (OCH=CH_2); NMR (benzene-d_6) resonances at δ 1.07 (3 H, triplet, J = 7 Hz, ethoxy methyl), 1.65 (3 H, singlet, acetyl methyl), 2.20–2.49 (4 H, multiplet, methylenes), 3.44 (2 H, quartet, J = 7 Hz, ethoxy methylene), 3.83 (1 H, doublet, J = 1 Hz, vinyl H), and 3.91 (1 H, doublet, J = 1 Hz, vinyl H); significant mass spectral fragmentations (with relative intensities) at m/e 142 (5, P), 99 (40), 71 (72), and 43 (100).

Anal. Calcd for $C_8H_{14}O_2$: M^+· 142.0994. Found: 142.1026.

10 and 11. 5-Ethoxyhex-4-en-2-one was isolable as two GLC fractions corresponding to the *E* and *Z* stereoisomers, which were not unambiguously distinguishable on the basis of spectral data (vide infra).

10. 5-Ethoxyhex-4-en-2-one A (71.2 min, yield 2%) was characterized by infrared (CS_2) absorptions at 3050 (sh, vinyl), 2980, 2920, 1715 (carbonyl), 1370, 1238, 1210, 1168, 1128, 1070, 962, and 790 cm^{-1}; NMR (benzene-d_6) resonances at δ 1.02 (3 H, triplet, J = 7 Hz, ethoxy methyl), 1.57 (3 H, singlet, vinyl methyl), 1.82 (3 H, singlet, acetyl methyl), 3.11 (2 H, doublet with unresolved fine splitting, J = 7 Hz, α-methylene), 3.45 (2 H, quartet, J = 7 Hz, ethoxy methylene), and 4.70 (1 H, broad triplet with unresolved fine splitting, J = 7 Hz, vinyl H); significant mass spectral fragmentations (with relative intensities) at m/e 142 (4, P), 99 (26), 71 (54), 43 (100), 29 (18), 31 (29), 27 (27), and 15 (19).

Anal. Calcd for $C_8H_{14}O_2$: M^+· 142.0994. Found: 142.0976.

11. 5-Ethoxyhex-4-en-2-one B (76.1 min, yield 3%) was characterized by infrared (CS_2) absorptions at 3080 (sh, vinyl), 2975, 2925, 2875, 1715 (carbonyl), 1660 (vinyl), 1385, 1360, 1313, 1240, 1215, 1163, 1127, 1080, 975, and 810 cm^{-1}; NMR (benzene-d_6) resonances at δ 1.14 (3 H, triplet, J = 7 Hz, ethoxy methyl), 1.75 (3 H, singlet, vinyl methyl), 1.78 (3 H, singlet, acetyl methyl), 2.77 (2 H, doublet, J = 7 Hz, α-methylene), 3.52 (2 H, quartet, J = 7 Hz, ethoxy methylene), and 4.57 (1 H, triplet with unresolved fine splitting, J = 7 Hz, vinyl); significant mass spectral fragmentations (with relative intensities) at m/e 142 (6, P) 99 (36), 71 (84), 43 (100), 29 (18), 27 (26), and 15 (19).

Anal. Calcd for $C_8H_{14}O_2$: M^+· 142.0994. Found: 142.1026.

Effects of Sensitizers and Quenchers. Samples were prepared and analyzed as for direct irradiations without additives (vide supra), except for addition of xanthone (0.19 M) or piperylene (0.9 M). Irradiation of xanthone-containing samples at 365 nm (Osram 1000-W super-pressure lamp, Schoeffel GM-250 monochromator, 23-nm bandwidth, xanthone absorbing all incident light) caused no reaction in 6.5 h. Using xanthone-sensitized piperylene isomerization as actinometer,[24–26] an upper limit for the quantum yield of disappearance of 3-ethoxy-3-methylpent-4-en-2-one was 4×10^{-3} mol/einstein.

With 0.9 M piperylene, samples irradiated with a Corex-D-filtered mercury lamp (Hanovia, 450 W) gave disappearance of 3-ethoxy-3-methylpent-4-en-2-one at a rate identical with that in parallel control samples. However, product yields were: acetaldehyde, 4%; 3-methylpent-4-en-2-one, 7%; (*Z*)-3-methylpent-3-en-2-one, 7%; (*E*)-3-methylpent-3-en-2-one, 9%; 2,3,4-trimethyl-2-vinyloxetanol A, 7%; 2,3,4-trimethyl-2-vinyloxetanol B, 3%; *dl*- and *meso*-3,4-dimethylhexane-2,5-diones, absent; 5-ethoxyhex-5-en-2-one, 5%; 5-ethoxyhex-4-en-2-one A, 4%; and 5-ethoxyhex-4-en-2-one B, 5%.

Photolysis of (*E*)-3-Methylpent-3-en-2-one with Acetaldehyde. A 1% solution of (*E*)-3-methylpent-3-en-2-one, 8 equiv of acetaldehyde, and 2% of *tert*-butylbenzene as standard in sodium-dried benzene-d_6 was irradiated with a Corex D-filtered 450-W medium-pressure Hanovia mercury arc lamp. Progress of the photolysis was followed by GLC (20 ft × 9 mm o.d. glass column, 5% SE-30 on 60/80 Chromosorb G-NAW, 85 °C, 95 mL/min) at 0, 15, 45, 90, and 150 min. After 15 min of irradiation the only photoproduct was (*Z*)-3-methylpent-3-en-2-one, identifiable by its GLC retention time.[15–18] After 150 min of irradiation more than 95% of the (*E*)- and (*Z*)-3-methylpent-3-en-2-ones had been destroyed and two products appeared which were *dl*- and *meso*-3,4-dimethylhexane-2,5-dione.

Photolysis of 5-Ethoxyhex-4-en-2-one A in Benzene-d_6. A 1% solution of 5-ethoxyhex-4-en-2-one A in sodium-dried benzene-d_6 was irradiated for 30 min with a Corex D-filtered medium-pressure Hanovia mercury arc lamp. Aliquots were analyzed at 0, 15, and 30 min of irradiation by GLC (20 ft × 9 mm o.d. glass column, 5% SE-30 on 60/80 Chromosorb G-NAW, 85 °C, 95 mL/min). After 30 min of irradiation three new GLC peaks were apparent, corresponding to 5-ethoxyhex-4-en-2-one B, 3-ethoxy-3-methylpent-4-en-2-one, and 5-ethoxyhex-5-en-2-one (64% of the A isomer had been destroyed). Integration of the GLC trace gave 5-ethoxyhex-4-en-2-one A, 3-ethoxy-3-methylpent-4-en-2-one, 5-ethoxyhex-4-en-2-one B, and 5-ethoxyhex-5-en-2-one in a ratio of 5.6:2.0:1.0:1.0. The GLC analysis was confirmed by ^1H FT NMR on an additional photolysate aliquot appropriately diluted with benzene-d_6.

Acknowledgment. Financial support furnished by the University of California, Davis, Committee on Research and by a Chancellor's Patent Fund grant to P.L.W. is gratefully acknowledged.

Registry No.—**6a**, 61769-86-6; **9**, 61769-87-7; **10**, 61769-88-8; **11**, 75-07-0; **12**, 758-87-2; *Z*-**13**, 1567-72-2; *E*-**13**, 1567-73-3; **14**, 61769-89-9; *dl*-**15**, 28895-03-6; *meso*-**15**, 28895-02-5; **16**, 61769-90-2; *Z*-**17**, 61769-91-3; *E*-**17**, 61769-92-4; ethyl iodide, 75-03-6.

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General Photochemical Synthesis of 1*H*-1,2-Benzodiazepines from *N*-Iminoquinolinium Ylide Dimers[1]

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Irradiation of *N*-iminoquinolinium ylide dimers **7a–i**, prepared from *N*-aminoquinolinium mesitylenesulfonates **5a–i** by treatment with base, in methylene chloride solution containing acetic acid afforded the fully unsaturated 1*H*-1,2-benzodiazepines **8a–i** in moderate yields. The photoproducts **8a** and **8c** were reduced with lithium aluminum hydride to the 2,3-dihydrobenzodiazepines **12a** and **12c**, which were further hydrogenated over palladium/carbon to give the 2,3,4,5-tetrahydrodiazepines **13a** and **13c**, respectively. The reduced 1,2-benzodiazepines gave the corresponding mono- (**14, 15**) and diacetyl (**16, 17**) derivatives. Based on NMR studies in $CDCl_3$–acetic acid solution which demonstrate an equilibrium between the dimers **7** and the corresponding *N*-iminoquinolinium ylides **6**, a mechanism for the formation of the 1,2-benzodiazepines **8** via the diaziridine (**25**) and 2*H*-1,2-benzodiazepine (**9**) intermediates is proposed.

Streith[2] first showed in 1968 that the photolysis of *N*-acyliminopyridinium ylides (**1**) yields the previously unknown 1*H*-1,2-diazepines (**2**) (Scheme I). Concurrent investigations by Sasaki[3] and by Snieckus,[4] and more recently by Abramovitch,[5] provided additional examples of this photoinduced ring expansion reaction. At present, this constitutes the only general route to simple, fully unsaturated 1*H*-1,2-diazepines.[6–8]

In contrast, the analogous *N*-acyliminoquinolinium (**3**)[9–11] and -isoquinolinium[10–12] ylides have been shown to rearrange upon irradiation into 2-aminoquinoline and 1-aminoisoquinoline derivatives, respectively, as well as to undergo N–N fragmentation to the respective parent heterocycles.[13] The formation of 1,2-benzodiazepines **4** from ylides **3** (Scheme I) as a result of photochemical ring expansion and solvent incorporation represents the two isolated exceptions to the above generalization.[9,10]

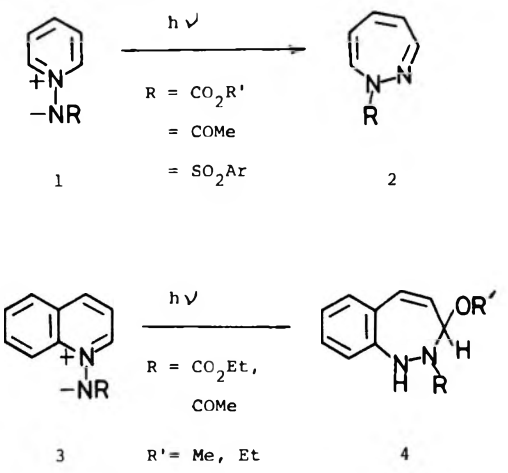
We report on the general photochemical synthesis of the hitherto unknown fully unsaturated 1*H*-1,2-benzodiazepines **8** from the *N*-iminoquinolinium ylide dimers **7**. Of the six theoretically possible benzodiazepines,[14] the 1,4-benzodiazepines have been most widely investigated owing to their useful biological activity.[15] The 1,5-benzodiazepines have also received substantial attention,[16] whereas the corresponding 1,3, 2,4, and 2,3 isomers have been neglected in comparison.[14,17] As for the 1,2 isomers, prior to the present work, only fused cyclopentano-3*H*-1,2-benzodiazepines had been reported.[18]

Table I. Preparation of 1*H*-1,2-Benzodiazepines (8)[a] by Irradiation of the *N*-Iminoquinolinium Ylide Dimers (7)

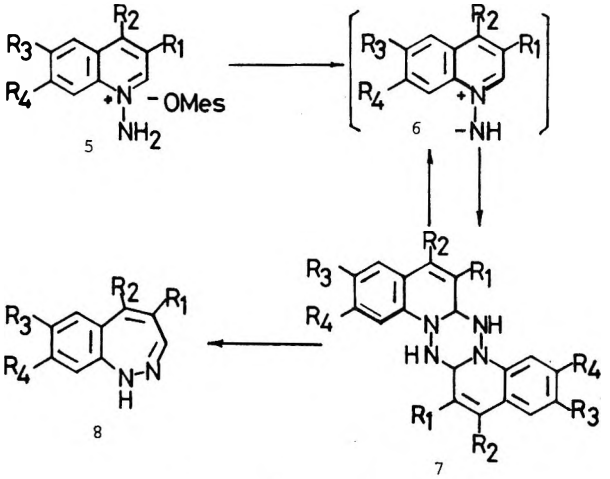
Registry no.	Compd	Reaction time, h	Yield,[b] %	Mp, °C[c]	NMR ($CDCl_3$), δ[h] 3-H	4-H	5-H	Misc[k]
264-60-8	**8a**	8	61	63–64[d]	7.07 (d)	5.97 (dd)[i]	6.86 (d)	
61702-22-5	**8b**	8	60	87–88[d]	6.97 (s)		6.65 (d)	1.92 (d, Me)[j]
54507-50-5	**8c**	10	79	63.5–64[e]	7.07 (d)	6.03 (m)		2.20 (br, Me)
59065-95-1	**8d**	9	47	94.5–95.5[f]	7.08 (d)	5.97 (dd)	6.89 (d)	2.24 (br, Me)
59065-96-2	**8e**	5	5	94.5–95.5[d]	7.08 (d)	6.02 (dd)	6.87 (d)	3.75 (s, OMe)
59065-97-3	**8f**	10	50	73–74[g]	7.05 (d)	5.94 (dd)	6.86 (d)	
61702-23-6	**8g**	15	38	114–115[d]	7.06 (d)	5.96 (dd)	6.88 (d)	3.90 (s, COOMe)
59065-99-5	**8h**	7	70	93.5–95[g]	7.05 (d)	5.92 (dd)	6.81 (d)	2.21 (br, Me)
59066-00-1	**8i**	20	62	103–104.5[g]	7.05 (d)	5.85 (dd)	6.79 (d)	3.77 (s, OMe)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all compounds listed. [b] Yields are of isolated products. [c] All compounds were recrystallized from isopropyl ether except **8g**, which was obtained from isopropyl ether–benzene. [d] Red prisms. [e] Yellow prisms. [f] Red plates. [g] Red needles. [h] See Experimental Section. Multiplicities are indicated by the usual symbols. [i] $J_{3,4}$ = 4 and $J_{4,5}$ = 11 Hz. [j] $J_{5,4\text{-Me}}$ = 1 Hz. [k] A broad signal (NH, δ 6.6–6.7) and multiplet signals (ArH, δ 6.2–8.0) appear in all spectra.

Scheme I



Scheme II



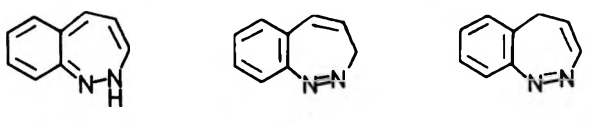
	R_1	R_2	R_3	R_4
a	H	H	H	H
b	Me	H	H	H
c	H	Me	H	H
d	H	H	Me	H
e	H	H	OMe	H
f	H	H	Cl	H
g	H	H	CO_2Me	H
h	H	H	H	Me
i	H	H	H	OMe

Results

The *N*-aminoquinolinium mesitylenesulfonates (**5**) (Scheme II) were prepared by N-amination of the corresponding quinolines with *O*-mesitylenesulfonylhydroxylamine according to the method of Tamura and co-workers.[10] Treatment of the salts **5** with potassium carbonate in dimethylformamide according to the method of Okamoto and co-workers[19] afforded in good yield the *N*-iminoquinolinium ylide dimers **7** presumably via the *N*-iminoquinolinium ylides **6**.

Irradiation of the dimers **7** in methylene chloride solution containing acetic acid resulted in the formation of the corresponding 1*H*-1,2-benzodiazepines **8** in the yields shown in Table I. In addition, small amounts of 2-aminoquinoline derivatives and parent quinolines were also isolated.

The reaction times, yields, and physical data of the new 1,2-benzodiazepines **8** are collected in Table I. The ^1H NMR spectral data, summarized in Table I, are consistent with the proposed structures and eliminate from further consideration the tautomeric 2*H*- (**9**), 3*H*- (**10**),[20] and 5*H*- (**11**) benzodi-

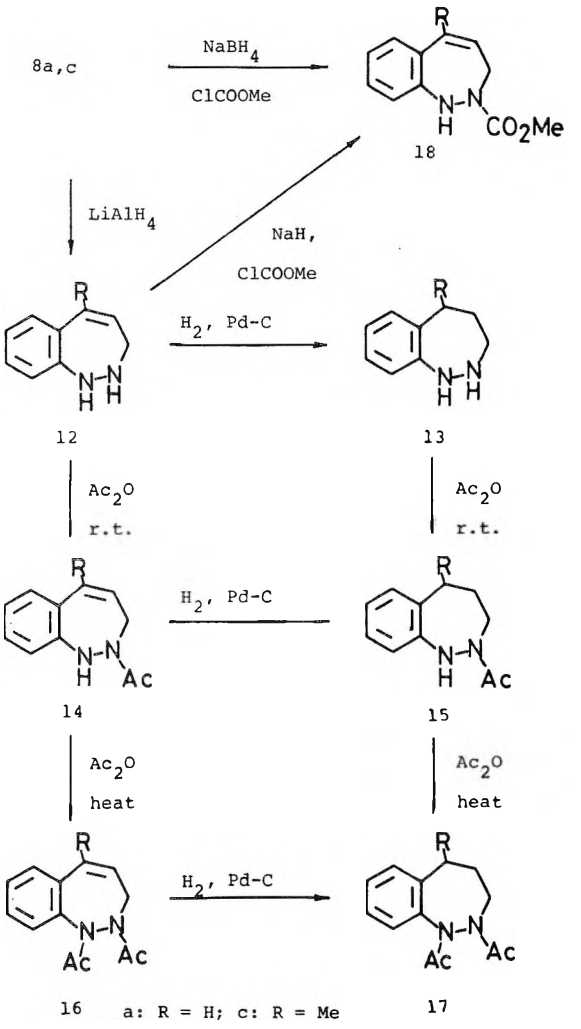


azepine structures as well as the diaziridine structure **25** (Scheme V). Complete characterization by IR, UV, and mass spectrometry was carried out for compounds **9a–c** (see Experimental Section). Further confirmation of structure was achieved by the following chemical studies.

Lithium aluminum hydride reduction of **8a,c** afforded in quantitative yields the 2,3-dihydrodiazepines **12a** and **12c**, respectively, which upon further catalytic hydrogenation gave the corresponding tetrahydrobenzodiazepines **13a** and **13c** (Scheme III). Treatment of **12a,c** and **13a,c** with acetic anhydride at room temperature provided the expected[21] 2-acetyl derivatives **14a,c** and **15a,c**, respectively, which upon reflux with the same reagent gave the corresponding 1,2-diacetyl-1,2-benzodiazepines **16a,c** and **17a,c**.[22] Compounds **16a,c** and **17a,c** could also be directly prepared from **12a,c** and **13a,c**, respectively, using the latter conditions. Catalytic hydrogenation of **14a,c** and **16a,c** yielded the tetrahydro derivatives **15a,c** and **17a,c**, respectively. Finally, acylation of **12a,c** with methyl chloroformate in the presence of sodium hydride af-

forded respectively the 2-methoxycarbonyl-2,3-dihydrobenzodiazepines **18a,c** which were also directly obtained from the photoproducts **8a,c** by reductive carbomethoxylation as shown in Scheme III.

Scheme III



Whereas the above metal hydride reduction proceeded without rupture of the heterocyclic ring, catalytic hydrogenation of **8a,c** resulted in the formation of the parent quinolines **21a,c** in 90% yields (Scheme IV). Since the formation of ammonia was detected, these reactions may proceed by initial reductive N–N bond fission to give **19a,c** which upon cyclization (**20a,c**) and elimination of ammonia leads to the quinoline derivatives **21a,c.**

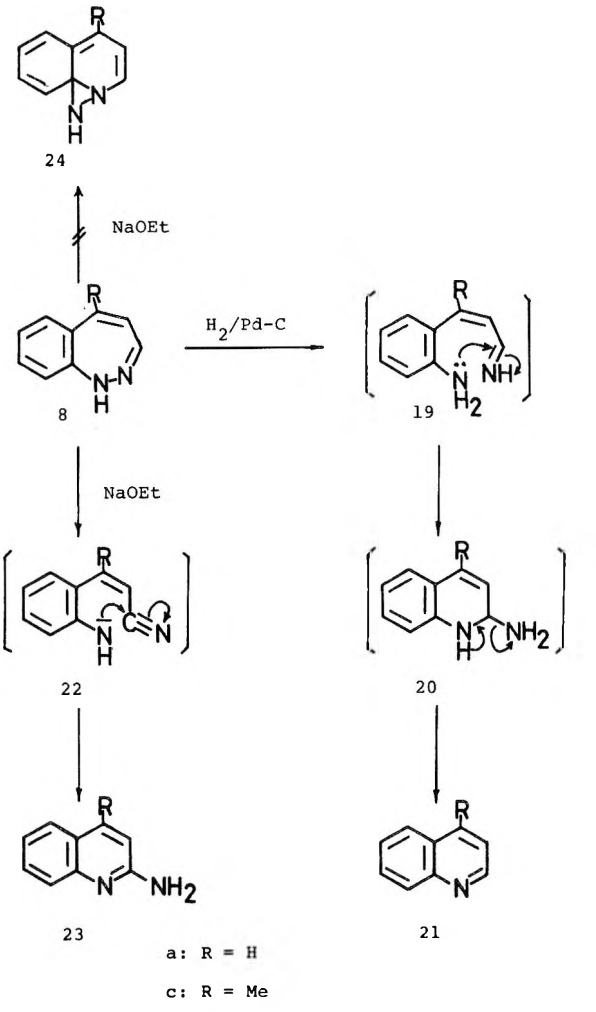
Ring contraction without expulsion of one nitrogen atom was observed when compounds **8a** and **8c** were subjected to treatment with excess sodium ethoxide in ethanol to give in high yield 2-aminoquinoline (**23a**) and 2-aminolepidine (**23c**), respectively. These results have excellent analogy to observations made with 1-acyl-1*H*-1,2-diazepines (**2**)[23] and may be similarly explained by invoking C-3 proton abstraction concomitant with N–N bond cleavage to give intermediate **22** which upon cyclization and tautomerization leads to the observed products **23a** and **23c.** The absence of quinoline products (**21a,c**) speaks against equilibration of **8a,c** with the energy-demanding, dearomatized diaziridine valence isomers **24a,c** under these reaction conditions. On the basis of previous observation,[24] the species **24a,c** would have been expected to lose nitrene fragments to give compounds **21a,c.**

The irradiation of *N*-iminoquinolinium ylide dimers **8a** and **8c** was studied in methylene chloride and in methylene chloride with added acetic acid and diethylamine, respectively.

Table II. Effect of Solvent on Product Yields in the Photolysis of Dimers 7a and 7c

Compd	Product	Yields, % CH_2Cl_2 AcOH	Solvent CH_2Cl_2	CH_2Cl_2 Et_2NH
	Diazepine **8a**	61	32	22
7a	Quinoline	7.5	18	28
	2-Aminoquinoline	0.1	1.5	3
	Diazepine **8c**	79	52	17
7c	Lepidine	4	13	17
	2-Aminolepidine		0.2	1.2

Scheme IV



The results of product distribution, summarized in Table II, show that the effect of diethylamine is to increase the amount of quinoline derivatives at the expense of the corresponding benzodiazepines. On the other hand, the formation of the benzodiazepines is increased and that of the quinolines is diminished in the presence of acetic acid.[25] Consequently, acetic acid has a favorable effect on the overall transformation **7** → **8.** Okamoto has previously shown that the *N*-iminoquinolinium ylides **6** formed by base treatment of the corresponding salts **5** are unstable and can only be isolated as the dimers **7.**[19] We now provide evidence that in $CDCl_3$–acetic acid solution these dimers exist in equilibrium with the ylides **6.**

The NMR spectrum of **7a** in $CDCl_3$ (Figure 1a) shows, aside from an unassigned multiplet at δ 6.4–7.5 (4 H), two doublets and one quartet in the region δ 5.4–5.8 (3 H) which are assigned to H_a, H_b, and H_c. Assignments were confirmed by

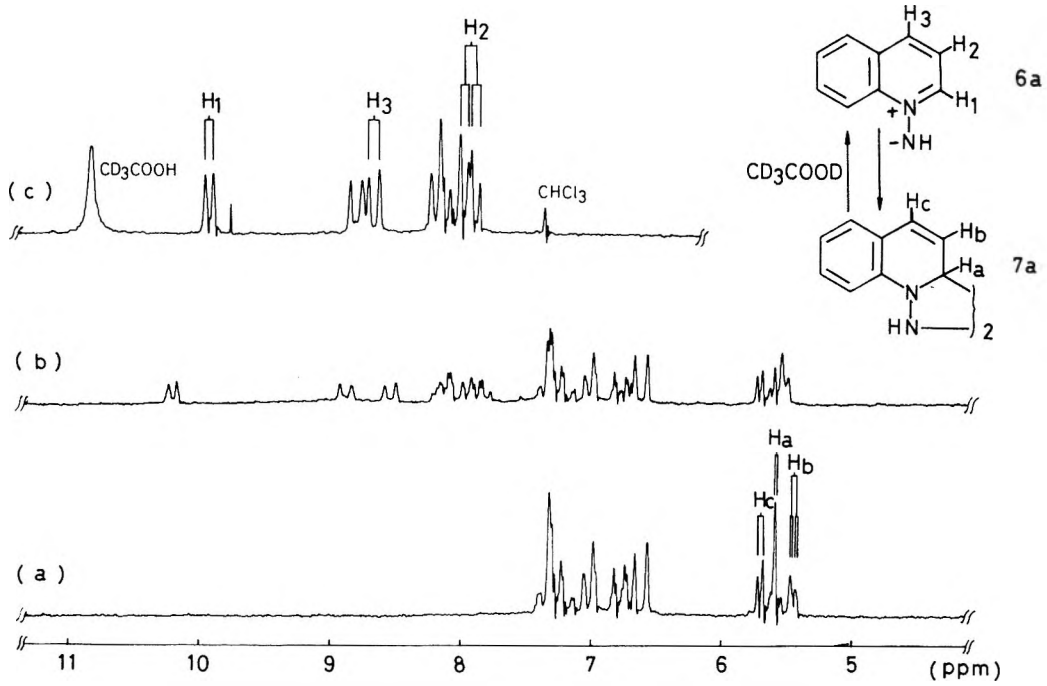


Figure 1. NMR spectra of **7a** in (a) $CDCl_3$ solution, (b) $CDCl_3$ solution containing 1 equiv of CD_3COOD, and (c) $CDCl_3$ solution containing 5 equiv of CD_3COOD.

spin-decoupling experiments. These spectral features are consistent with the presence of dimer **7a** in $CDCl_3$ solution. However, in $CDCl_3$ containing 1 molar equiv of acetic acid (Figure 1b), the spectrum is significantly different in that a number of new signals appear at low field. A limiting spectrum was observed upon addition of 5 molar equiv of acetic acid (Figure 1c) which no longer showed evidence for the presence of the dimer **7a** and instead exhibited a distinct set of signals consistent with the presence of the monomeric structure **6a**: δ 9.85 (d, H_1), 7.86 (dd, H_2), 8.58 (d, H_3), 8.90 (d, H_8), and 7.9–8.25 (m, H_4, H_5, and H_6), $J_{1,2} = 6$ and $J_{2,3} = 8$ Hz. Strong support for these proton assignments and thus for structure **6a** was obtained by spectral comparison with *N*-ethoxycarbonyliminoquinolinium ylide,[19] which shows δ 9.35 (d, H_1), 7.63 (dd, H_2), 8.34 (d, H_3), 8.92 (d, H_8), and 7.7–8.1 (m, H_4, H_5, and H_6), $J_{1,2} = 6$ and $J_{2,3} = 8$ Hz.

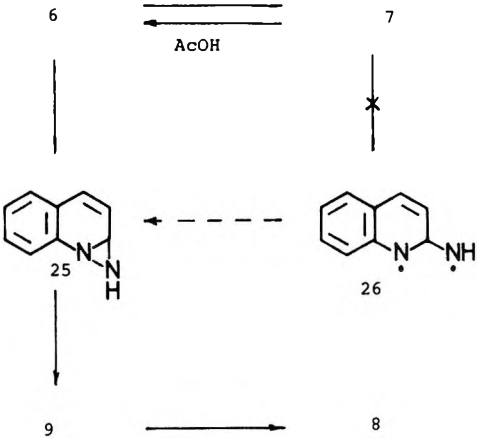
Discussion

On the basis of the above results, we suggest that methylene chloride–acetic acid solutions of dimer **7** contain equilibrium concentrations of *N*-iminoquinolinium ylide **6** and that it is this species which, by analogy with previous mechanistic proposals for the photochemical rearrangement of *N*-acyliminopyridinium ylides,[6a] undergoes internal 1,3-photocycloaddition to give the diaziridines **25** and then valence tautomerization to yield the o-quinonoid 2*H*-1,2-benzodiazepine **9**.[26] Aromatic stability considerations would dictate that the latter would rapidly undergo a photochemically allowed [1,7] sigmatropic hydrogen shift to give the observed product (**8**) (Scheme V).

Schmitz and Ohme[27] have reported that the pyrolysis of 3,4-dihydro-*N*-iminoisoquinolinium ylide dimer gives 4,5-dihydro-3*H*-2,3-benzodiazepine. This reaction may be reasonably envisaged to proceed via a diradical intermediate resulting initially from homolytic N–N bond fission. In the present photochemical reaction, the thermal formation of diaziridine **25** from dimer **7** via the intermediate diradical **26** is unlikely in view of the fact that separate pyrolysis of **7** gave the parent quinoline as the sole product without detectable amounts of ring expansion or rearrangement products.

Examination of Table I does not reveal a qualitative trend

Scheme V



in the effect of substituents on the photochemical rearrangement. Thus electron-donating substituents at C_4 and C_7 provide good yields of benzodiazepines (**8c, 8h, 8i**), whereas both electron-donating and -withdrawing groups at C_6 give lower or poor yields of products (**8d–g**). In view of the small number of cases studied and the potential variation in the photochemical instability of the products as a function of substituent, no conclusions regarding these effects can be drawn at this time.

Finally, a number of other 2- and 4-substituted *N*-aminoquinolinium salts (2-Me, 2-Cl, 2-Ph, 4-Cl, 4-NO_2, 4-OMe) were also prepared. However, upon treatment with base, these did not yield the corresponding dimers. Attempts to obtain benzodiazepines by treatment of the salts with aqueous potassium carbonate–methylene chloride followed by irradiation of the organic phase (presumably containing the *N*-iminoquinolinium ylides) were not successful.

In conclusion, we have described a photochemical synthetic entry into the previously unknown 1*H*-1,2-benzodiazepines (**8**) class of heterocycles. These compounds are now available for further physicochemical studies. An analogous preparative route for 2,3-benzodiazepines from *N*-aminoisoquinolinium salts has not been successful to date.

Table III. *N*-Aminoquinolinium Mesitylenesulfonates (5) and *N*-Iminoquinoline Dimers (7)[a]

Compd	5			7		
	Mp, °C	Yield, %	Registry no.	Mp, °C	Yield, %	Registry no.
a	131–133[b]	94	39996-55-9	154–156[c]	62	7184-52-3
b	136–137	92	61702-25-8	187–188	84	61702-36-1
c	151–152	96	57489-82-4	186–187	56	54507-49-2
d	142–143	94	61702-27-0	155–157	77	59066-14-7
e	163–165	95	61740-70-3	142–145	55	59066-15-8
f	229–231	93	61702-29-2	184–186	86	59066-16-9
g	192–194	89	61702-31-6	200–202	93	61702-37-2
h	217–219	94	61702-33-8	149–150	52	59066-18-1
i	170–172	95	61702-35-0	154–156	59	59066-19-2

[a] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all new compounds listed in the table. [b] Lit.[10] mp 132–133 °C. [c] Lit.[19] mp 155–156 °C.

Experimental Section

Melting points were measured on a Yamato Model MP-21 apparatus and are uncorrected. Infrared spectra were determined in KBr pellets with a JASCO IRA-2 spectrophotometer. Mass spectra were obtained on a JEOL-D100 instrument. NMR spectra were recorded on Hitachi R-20, R-22, and JEOL JNM-MH-100 spectrometers in deuteriochloroform solution using tetramethylsilane as internal standard unless otherwise stated. Spectral assignments were confirmed by spin-decoupling experiments and, in the case of NH protons, by exchange with D_2O. Ultraviolet spectra were recorded on a Hitachi Model 323 spectrophotometer in ethanol solution. Microanalyses were performed by the Microanalytical laboratory, Showa University, Tokyo, Japan. Column and thin layer chromatography were carried out with alumina and silica gel obtained from Merck Co. Ltd.

Photolyses were carried out under a nitrogen atmosphere using an immersion apparatus equipped with a 400-W high-pressure mercury lamp (Nikko Sekiei Co., Japan) and a Pyrex filter, which was cooled internally with running water.

Materials. Quinoline, 4-, 6-, and 7-methylquinoline, 6-chloroquinoline, 2-aminoquinoline, and 2-aminolepidine were obtained from Tokyo Kasei Kogyo Co., Japan. 3-Methyl-,[28] 6-methoxy-,[29] 6-methoxycarbonyl-,[30] and 7-methoxyquinoline[31] were prepared by literature procedures.

Preparation of *N*-Aminoquinolinium Mesitylenesulfonates (5a–i). General Procedure. The procedure of Tamura and coworkers[10] for the preparation of **5a** was employed. A solution of *O*-mesitylenesulfonylhydroxylamine (0.11 mol) in methylene chloride (150 mL) was added dropwise to a solution of quinoline derivative (0.1 mol) in methylene chloride (100 mL) with constant stirring in an ice bath. The reaction mixture was stirred further for 30 min at room temperature and then cooled in an ice bath. After addition of ether (200–500 mL) to the mixture, the resulting crystalline precipitate was collected and recrystallized from ethanol or ethanol–ethyl acetate to give the salt (**5**).

The results are presented in Table III.

Preparation of *N*-Iminoquinoline Dimers (7a–i). General Procedure. The procedure was adapted from that of Okamoto and co-workers.[19]

To a solution of the *N*-aminoquinolinium salt (**5**, 70 mmol) in dimethylformamide (200–300 mL) was added solid potassium carbonate (10.6 g, 77 mmol) in small portions with stirring at room temperature. After stirring for an additional 2 h, 300–600 mL of ice-cooled water was added slowly to the reaction mixture. The resulting crystalline precipitate was collected by filtration and washed with cold water and then with several portions of methanol to give the dimer (**7**), which was used in the following photolysis without further purification. Further reprecipitation with 5% aqueous potassium hydroxide solution from an aqueous 5% hydrogen chloride solution of the dimer furnished an analytical sample. The results are presented in Table III.

Preparation of 1*H*-1,2-Benzodiazepines (8a–i). General Photolysis Procedure. A solution of the dimer **7** (5 mmol) and acetic acid (3 g, 50 mmol) in methylene chloride (300 mL) was irradiated under a nitrogen atmosphere. The photolysis was followed by the disappearance of the absorption at 230–250 nm due to **7** in the UV spectrum and was complete in 5–20 h. After acetic acid was removed by extraction with saturated aqueous sodium bicarbonate, the reaction solution was washed with water, dried over $MgSO_4$, and evaporated to dryness. The resulting residue was chromatographed over alumina using *n*-hexane–methylene chloride (1:1) as eluent. Recrystallization from isopropyl ether–benzene gave the diazepines (**8**).

Reaction times of the photolysis, yields, and physical data of **8** are collected in Table I. NMR spectral data are also collected in Table I while salient IR and mass spectral data of **8a–c** are described below. **8a:** 3270 cm^{-1} (NH); mass spectrum *m/e* (rel intensity) 144 (M^+, 100); 117 (68), and 116 (11); λ_{max} (ϵ) 250 nm (17 000). **8b:** 3270 cm^{-1} (NH); mass spectrum *m/e* (rel intensity) 158 (M^+, 100), 131 (64), and 130 (80); λ_{max} (ϵ) 245 nm (16 000). **8c:** 3290 cm^{-1} (NH); mass spectrum *m/e* (rel intensity) 158 (M^+, 100), 131 (27), and 130 (73); λ_{max} (ϵ) 246 nm (16 000).

2,3-Dihydro-1*H*-1,2-benzodiazepine (12a). To a suspension of $LiAlH_4$ (0.5 g) in anhydrous ether (100 mL) cooled in an ice bath was added dropwise a solution of the diazepine **8a** (1.0 g) in ether (50 mL) with stirring. The mixture was allowed to warm to room temperature and was stirred for an additional 15 min. The reaction mixture was cooled in an ice bath and the excess reagent was decomposed with water. After removal of the resulting inorganic salts by filtration, the ether solution was dried ($MgSO_4$) and evaporated to dryness to give **12a:** colorless needles (isopropyl ether); 970 mg (96%); mp 56–58 °C; ν 3240 cm^{-1} (NH); mass spectrum *m/e* 146 (M^+); δ 3.5 (1 H, br, NH), 3.75 (2 H, m, 3-H), 5.7 (1 H, br, NH), 5.95 (1 H, m, 4-H), 6.40 (1 H, m, 5-H), and 6.6–7.5 (4 H, m, Ar-H), $J_{3,4}$ = 3, $J_{3,5}$ = 1, and $J_{4,5}$ = 13 Hz.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.03; H, 6.81; N, 19.36.

5-Methyl-2,3-dihydro-1*H*-1,2-benzodiazepine (12c). The reaction of 5-methyl-1,2-benzodiazepine (**8c**, 1.0 g) with $LiAlH_4$ (0.5 g) was carried out and worked up in the same manner as described for **12a** to give **12c:** colorless needles (isopropyl ether); 954 mg (94%); mp 75–76 °C; ν 3230 cm^{-1} (NH); mass spectrum *m/e* 160 (M^+); δ 2.13 (3 H, m, 5-Me), 3.72 (2 H, m, 3-H), 4.1 (2 H, br, NH), 5.98 (1 H, m, 4-H), and 6.5–7.6 (4 H, m, Ar-H), $J_{3,4}$ = 3 and $J_{3,5\text{-Me}} = J_{4,5\text{-Me}}$ = 1 Hz.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49. Found: C, 75.05; H, 7.41; N, 17.63.

2,3,4,5-Tetrahydro-1*H*-1,2-benzodiazepine (13a). A solution of **12a** (276 mg) in methanol (10 mL) was hydrogenated with 5% Pd/C (300 mg) with stirring under atmospheric pressure at room temperature. The reaction mixture was subjected to filtration and the filtrate was evaporated to dryness in vacuo. After treating with active charcoal in benzene, the residue was recrystallized from isopropyl ether–*n*-hexane to give **13a:** colorless needles; 252 mg (90%); mp 56–57 °C; ν 3320 cm^{-1} (NH); mass spectrum *m/e* 148 (M^+); δ 1.5–2.6 (2 H, m, 4-H), 2.7–3.3 (2 H, m, 5-H), 2.8–4.0 (2 H, m, 3-H), 4.1 (2 H, br, NH), and 6.6–7.5 (4 H, m, ArH).

Anal. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 73.16; H, 8.08; N, 19.07.

5-Methyl-2,3,4,5-tetrahydro-1*H*-1,2-benzodiazepine (13c). A solution of **12c** (240 mg) was hydrogenated with 5% Pd/C (300 mg) and worked up in a similar manner as that described for the preparation of **13a** to give **13c:** colorless needles (isopropyl ether–*n*-hexane); 209 mg (86%); mp 45–46 °C; ν 3270 cm^{-1} (NH); mass spectrum *m/e* 162 (M^+); δ 1.33 (3 H, d, J = 7 Hz, 5-Me), 1.0–2.0 (2 H, m, 4-H), 2.9–3.3 (3 H, m, 3-H and 5-H), 3.3 (1 H, br, NH), and 6.5–7.4 (4 H, m, ArH).

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.91; H, 8.63; N, 17.22.

2-Acetyl-2,3-dihydro-1*H*-1,2-benzodiazepine (14a). A mixture

of **12a** (276 mg) and acetic anhydride (6 mL) was stirred at room temperature overnight. The reaction mixture was evaporated to dryness in vacuo below 60 °C and the residue was dissolved in methylene chloride (150 ml). The solution was washed with saturated aqueous sodium bicarbonate and then with water, dried over $MgSO_4$, and evaporated. The resulting residue was chromatographed over alumina using methylene chloride–*n*-hexane (1:1) as eluent to give **14a:** colorless prisms (isopropyl ether); 315 mg (89%); mp 108–109 °C; ν 3260 (NH) and 1640 cm^{-1} (C=O); mass spectrum *m/e* 188 (M^+); δ 2.01 and 2.14 (3 H, s, Ac-Me), 4.3–4.6 (2 H, m, 3-H), 5.5–6.0 (1 H, m, 4-H), 6.2–6.6 (1 H, m, 5-H), 6.6 (1 H, br, NH), and 6.7–7.3 (4 H, m, Ar-H), $J_{3,4}$ = 4, $J_{3,5}$ = 1, and $J_{4,5}$ = 12 Hz.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.06; H, 6.15; N, 14.62.

2-Acetyl-5-methyl-2,3-dihydro-1*H*-1,2-benzodiazepine (14c). The diazepine **12c** (316 mg) was acetylated with acetic anhydride (6 mL) at room temperature by a procedure similar to that described for the preparation of **14a** to give **14c:** colorless prisms (benzene–isopropyl ether); 370 mg (93%); mp 89–90 °C; ν 3270 (NH) and 1645 cm^{-1} (C=O); mass spectrum *m/e* 202 (M^+); δ 2.06 and 2.15 (3 H, s, Ac-Me), 2.20 (3 H, m, 5-Me), 4.1–4.5 (2 H, m, 3-H), 5.6–6.1 (1 H, m, 4-H), 5.9 (1 H, br, NH), and 6.9–7.5 (4 H, m, ArH).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.97; 6.85; N, 13.99.

2-Acetyl-2,3,4,5-tetrahydro-1*H*-1,2-benzodiazepine (15a). From 13a. A mixture of **13a** (128 mg) and acetic anhydride (6 mL) was allowed to react and worked up in the same manner as described for **14a** to give **15a:** colorless prisms (isopropyl ether); 125 mg (76%); mp 100–102 °C; ν 3280 (NH) and 1630 cm^{-1} (C=O); mass spectrum *m/e* 190 (M^+); δ 2.05 and 2.12 (3 H, s, Ac-Me), 1.7–2.2 (2 H, m, 4-H), 2.6–3.1 (2 H, m, 5-H), 3.6–4.0 (2 H, m 3-H), 6.7–7.3 (4 H, m, ArH), and 7.1 (1 H, br, NH).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.26; H, 7.24; N, 14.61.

From 14a. A solution of **14a** (100 mg) in methanol (10 mL) was hydrogenated in the presence of 5% Pd/C (100 mg) and worked up in a manner similar to that described for the preparation of **13a** to give 98 mg (97%) of **15a.**

2-Acetyl-5-methyl-2,3,4,5-tetrahydro-1*H*-1,2-benzodiazepine (15c). From 13c. A mixture of **13c** (67 mg) and acetic anhydride (3 mL) was allowed to react and worked up in a manner similar to that described for **14a** to give **15c:** colorless prisms (isopropyl ether–benzene); 72 mg (89%); mp 113.5–115 °C; ν 3300 (NH) and 1640 cm^{-1} (C=O); mass spectrum *m/e* 204 (M^+); δ 1.25 and 1.38 (3 H, d, 5-Me), 1.6–2.2 (2 H, m, 4-H), 2.05 and 2.10 (3 H, s, Ac-Me), 2.9–3.6 (1 H, m, 5-H), 3.7–4.0 (2 H, m, 3-H), 6.8–7.3 (4 H, m, ArH), and 7.0 (1 H, br, NH), $J_{5,5\text{-Me}}$ = 7 Hz.

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.49; H, 7.76; N, 13.98.

From 14c. A solution of **14c** (100 mg) in methanol (10 mL) was hydrogenated in the presence of 5% Pd/C (100 mg) and worked up as described for **13a** to give 97 mg (96%) of **15c.**

1,2-Diacetyl-2,3-dihydro-1*H*-1,2-benzodiazepine (16a). A mixture of **14a** (200 mg) and acetic anhydride (8 mL) was refluxed for 4 h and evaporated to dryness in vacuo. The residue was dissolved in methylene chloride (100 mL) and the resulting solution was successively washed with sodium bicarbonate solution and water and evaporated to dryness. The resulting residue was chromatographed over alumina using *n*-hexane–methylene chloride (1:1) as eluent to give **16a:** colorless prisms (isopropyl ether–benzene); 224 mg (91%); mp 78–80 °C; ν 1660 (C=O) and 1695 cm^{-1} (C=O); mass spectrum *m/e* 230 (M^+); δ 2.04, 2.08, and 2.23 (6 H, s, Ac-Me), 4.0–5.6 (2 H, m, 3-H), 5.7–6.1 (1 H, m, 4-H), 6.3–6.7 (1 H, m, 5-H), and 7.2–7.5 (4 H, m, ArH).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.71; H, 6.02; N, 12.49.

1,2-Diacetyl-5-methyl-2,3-dihydro-1*H*-1,2-benzodiazepine (16c). Compound **14c** (300 mg) was acetylated under conditions similar to those described for the preparation of **16a** to give **16c:** colorless prisms (isopropyl ether–benzene); 336 mg (94%); mp 104.5–105.5 °C; ν 1665 (C=O) and 1700 cm^{-1} (C=O); mass spectrum *m/e* 244 (M^+); δ 1.88, 1.95, 2.08, and 2.30 (6 H, s, Ac-Me), 2.1 (3 H, m, 5-Me), 4.0–5.1 (2 H, m, 3-H), 5.5–5.9 (1 H, m, 4-H), and 6.8–7.5 (4 H, m, ArH).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.95; H, 6.47; N, 11.61.

1,2-Diacetyl-2,3,4,5-tetrahydro-1*H*-1,2-benzodiazepine (17a). From 15a. A mixture of **15a** (80 mg) and acetic anhydride (8 mL) was allowed to react and worked up in the same manner as described for the preparation of **16a** to give **17a:** colorless prisms (isopropyl ether–benzene); 88 mg (90%); mp 91–93 °C; ν 1670 cm^{-1} (C=O); mass spectrum *m/e* 232 (M^+); δ 2.03, 2.13, 2.16, and 2.29 (6 H, s, Ac-Me), 1.6–2.3 (2 H, m, 4-H), 2.8–3.5 (3 H, m, 3-H and 5-H), 4.6–5.1 (1 H, m, 3-H), and 7.2–7.5 (4 H, m, ArH).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 6.86; N, 11.93.

From 16a. A solution of **16a** (45 mg) in methanol (8 mL) was hydrogenated over 5% Pd/C (45 mg) and worked up as described for the preparation of **13a** to give 44 mg (97%) of **17a.**

1,2-Diacetyl-5-methyl-2,3,4,5-tetrahydro-1*H*-1,2-benzodiazepine (17c). From 15c. A mixture of **15c** (57 mg) and acetic anhydride (5 mL) was allowed to react and worked up in the same manner as described for the preparation of **16a** to give **17c:** colorless prisms (isopropyl ether–benzene); 65 mg (94%); mp 115–117 °C; ν 1680 cm^{-1} (C=O); mass spectrum *m/e* 246 (M^+); δ 1.13, 1.32, 1.37, and 1.43 (3 H, d, 5-Me), 1.80, 2.02, 2.04, 2.11, 2.13, 2.16, 2.32, and 2.35 (6 H, s, Ac-Me), 1.6–2.3 (2 H, m, 4-H), 3.0–3.6 (3 H, m, 3-H and 5-H), 4.4–4.9 (1 H, m, 3-H), and 7.2–7.3 (4 H, m, ArH).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.18; H, 7.20; N, 11.00.

From 16c. A solution of **16c** (50 mg) in methanol (8 mL) was hydrogenated over 5% Pd/C (50 mg) and worked up in the manner described for the preparation of **13a** to give 49 mg (97%) of **17c.**

2-Methoxycarbonyl-2,3-dihydro-1*H*-1,2-benzodiazepine (18a). From 12a. To a mixture of **12a** (280 mg), sodium hydride (50% in paraffin oil, 213 mg), and tetrahydrofuran (15 mL) cooled in an ice bath was added dropwise with stirring a solution of methyl chloroformate (420 mg) in tetrahydrofuran (5 mL). The reaction mixture was stirred for 2 h and evaporated to dryness in vacuo below 40 °C. The residue was dissolved in cold water (20 mL) and the resulting solution was extracted with methylene chloride. The organic extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed over alumina using benzene as eluent to give **18a:** colorless plates (isopropyl ether); 260 mg (67%); mp 109–110 °C; ν 3280 (NH) and 1680 cm^{-1} (C=O); mass spectrum *m/e* 204 (M^+); δ 3.06 (3 H, s, CO_2Me), 4.45 (2 H, m, 3-H), 5.75 (1 H, m, 4-H), 6.35 (1 H, m, 5-H), 6.2 (1 H, br, NH), and 6.6–7.25 (4 H, m, ArH), $J_{3,4}$ = 3, $J_{3,5}$ = 1.5, and $J_{4,5}$ = 12 Hz.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 5.75; N, 13.79.

From 8a. To a solution of **8a** (144 mg) and $NaBH_4$ (190 mg) in tetrahydrofuran (15 mL) cooled in an ice bath was added dropwise with stirring a solution of methyl chloroformate (120 mg) in tetrahydrofuran (5 mL). After further stirring for 1 h at room temperature, the reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in water (20 mL) and the resulting solution was extracted with methylene chloride. The organic extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed over silica gel using methylene chloride as eluent to give 89 mg (44%) of **18a.**

2-Methoxycarbonyl-5-methyl-2,3-dihydro-1*H*-1,2-benzodiazepine (18c). From 12c. A mixture of **12c** (291 mg), sodium hydride (213 mg), and tetrahydrofuran (15 mL) was treated with a solution of methyl chloroformate (420 mg) under conditions similar to those described for the preparation of **18a.** Similar workup gave **18c:** colorless plates (isopropyl ether); 310 mg (79%); mp 100–101 °C; ν 3280 and 3310 (NH) and 1700 cm^{-1} (C=O); mass spectrum *m/e* 218 (M^+); δ 2.15 (3 H, m, 5-Me), 3.60 (3 H, s, CO_2Me), 4.40 (2 H, m, 3-H), 5.78 (1 H, m, 4-H), 6.3 (1 H, br, NH), and 6.9–7.5 (4 H, m, ArH), $J_{3,4}$ = 4 and $J_{3,5\text{-Me}}$ = 1.5 Hz.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.13; H, 6.29; N, 12.66.

From 8c. A solution of **8c** (158 mg) and $NaBH_4$ (190 mg) in tetrahydrofuran was treated with methyl chloroformate (120 mg) according to the conditions used for the preparation of **18a.** Similar workup gave 103 mg (48%) of **18c.**

Reaction of 1*H*-1,2-Benzodiazepines (8a,c) with Sodium Ethoxide. To a solution of 8 (150 mg) in ethanol (15 mL) was added excess sodium ethoxide (70 mg) and the mixture was refluxed for 20 h. After removal of the solvent in vacuo, water (20 mL) was added to the residue and the mixture was extracted with methylene chloride. The extract was dried ($MgSO_4$) and evaporated to dryness. The resulting residue was recrystallized from benzene to give 2-aminoquinoline derivative (**23**) which was shown to be identical with an authentic sample by melting point and mixture melting point comparison.

From **8a:** 2-aminoquinoline (**23a**), 138 mg (92%), mp 134–135 °C.

From **8c:** 2-aminolepidine (**23c**), 131 mg (87%), mp 131–133 °C.

Catalytic Reduction of 1*H*-1,2-Benzodiazepines (8a,c). The diazepine 8 (1.0 mmol) was hydrogenated over 5% Pd/C (150 mg) in

methanol (10 mL) with stirring at room temperature under atmospheric pressure. After uptake of ca. 1 mmol of hydrogen, the reaction was stopped. The reaction mixture, exhibiting a strong odor of ammonia, was evaporated to dryness in vacuo and the residue was purified by short-path distillation under reduced pressure to give the parent quinoline which was characterized as its picrate.

From **8a** (144 mg): quinoline, 121 mg (94%).

From **8c** (158 mg): lepidine, 127 mg (89%).

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Registry No.—**6a,** 59046-19-4; **12a,** 55379-60-7; **12c,** 54507-51-6; **13a,** 59066-24-9; **13c,** 59066-25-0; **14a,** 59066-20-5; **14c,** 59066-21-6; **15a,** 59066-22-7; **15c,** 59066-23-8; **16a,** 59066-26-1; **16c,** 59066-27-2; **17a,** 59066-28-3; **17c,** 59066-29-4; **18a,** 61702-38-3; **18c,** 54507-52-7; **23a,** 580-22-3; **23c,** 27063-27-0; methyl chloroformate, 79-22-1.

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Amidrazones. 4.[1] Ylide Syntheses

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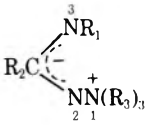
Aminimides derived from imidic acids (**3**) are conveniently prepared by the reaction of molar equivalents of a nitrile, 1,1,1-trimethylhydrazinium chloride (or tosylate), and KO-*t*-Bu in refluxing *t*-BuOH. Alkylation of 1,1,1-trimethyl-2-acetimidoylhydrazinium hydroxide inner salt (**3a**) with MeI and EtI gave N^3-alkylated salts which afforded N^3-substituted ylides (**6**) on neutralization. Reaction of 1,1,1-trimethyl-2-α-methoxybenzylidenehydrazinium tosylate (**11**) with either aniline or benzylamine gave 1,1-dimethyl-2-α-methoxybenzylidenehydrazine (**12**).

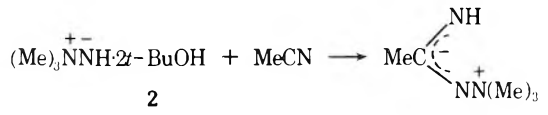
This paper summarizes the results of our study of preparative procedures for amidrazone ylides. These compounds, which may also be classified as aminimides[2] derived from imidic acids, are represented by the general structure **1**. The recommended[3] method for numbering the nitrogen atoms in amidrazones is also designated in structure **1** and is used throughout this paper.



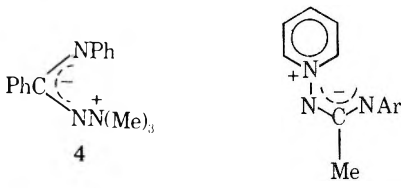
1

The preparation of ylides of type **1** has received scant attention. Appel and co-workers[4] have reported the preparation of 1,1,1-trimethyl-2-acetimidoylhydrazinium hydroxide inner salt (**3a**) by the addition of the *tert*-butyl alcohol complex of 1,1,1-trimethylhydrazinium hydroxide inner salt (**2**) to acetonitrile. We have previously reported[1] the preparation of ylide **4** by the reaction of **2** (generated in situ) with *N*-phenylbenzimidoyl chloride. Recently, Abramovitch and coworkers[5] obtained pyridinium ylides (**5**) by neutralization of the salts obtained by the reaction of 1-aminopyridinium fluoroborates with aryldiazonium fluoroborates in acetonitrile.

Subsequent to our communication describing the prepa-



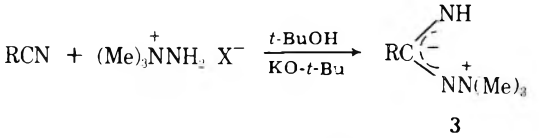
2 3a



4 5

ration and properties of **4**, a modified procedure was developed that resulted in a 72% yield of ylide. The improved procedure is described in the Experimental Section. Attempted preparation of the N^3-methyl analogue of this compound by reaction of *N*-methylbenzimidoyl chloride with **2** resulted in complex, tarry mixtures.

A serious disadvantage to the preparation of ylides of type **3** via Appel's[4] procedure is the difficulty encountered in the preparation of **2**, which is an extremely hygroscopic solid that requires rigorous exclusion of moisture for its successful preparation from 1,1,1-trimethylhydrazinium chloride and KO-*t*-Bu in THF containing *t*-BuOH. We have found that a variety of ylides of type **3** can be conveniently prepared by a procedure that generates **2** in situ. The modified procedure simply involves reaction of molar equivalents of a nitrile, 1,1,1-trimethylhydrazinium chloride (or tosylate), and KO-*t*-Bu in refluxing *t*-BuOH.



3

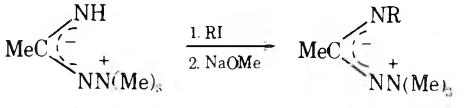
$X^- = Cl^-$ or TsO^-

a, R = Me	d, R = 4-ClC_6H_4
b, R = Et	e, R = 4-$MeOC_6H_4$
c, R = Ph	f, R = 3-pyridyl

The ylides prepared by the above procedure were obtained as extremely hygroscopic solids or oils that, with the exception of **3c**, could not be obtained analytically pure. However, all of the ylides displayed NMR spectra that support the assigned structures and were further characterized by conversion to picrate or hydrohalide salts.

The ylides are strongly basic compounds. Compound **3c** has $pK_b = 1.93$ (±0.03) and chloroform solutions of this compound darkened on standing and deposited the hydrochloride of **3c**. Apparently the basic ylide is capable of initiating α-elimination on chloroform.

Compound **3a** was alkylated in good yield with methyl and ethyl iodide to give, after neutralization, N^3-alkyl-substituted ylides (**6**).



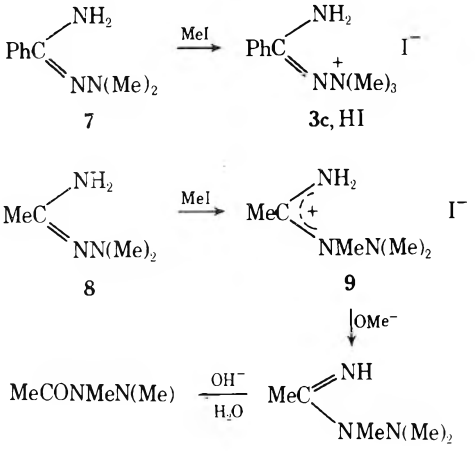
3a 6

a, R = Me; b, R = Et

Attempted alkylation of **3c** with methyl iodide and **3a** with *n*-propyl iodide and benzyl chloride resulted in the formation of mixtures from which, in each case, only the conjugate acid (hydrohalide) of the starting material could be isolated.

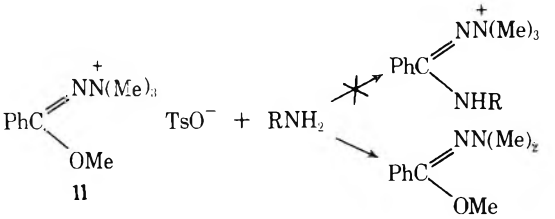
As an alternate approach to the synthesis of ylides of type **3**, we have examined the methylation of amidrazones **7** and **8** since alkylation of these compounds at N^1 would provide the conjugate acids of **3**. Although we have previously studied the alkylation of a variety of amidrazones,[6] our study did not include N^3-unsubstituted compounds. Treatment of **7** with methyl iodide resulted in a mixture from which the N^1-alkylated product (**3c** HI) was isolated in low yield. However **8** proved to be an unsuitable candidate for ylide synthesis since on treatment with methyl iodide the N^2-alkylated material (**9**) was produced in good yield. The structure of **9** was established by hydrolysis of the unstable free base (**10**) to 1,1,2-trimethyl-2-acetylhydrazine.

Scheme I



7 3c, HI 8 9 10

We have also attempted the preparation of the conjugate acids of amidrazone ylides by the reaction of 1,1,1-trimethyl-2-α-methoxybenzylidenehydrazinium tosylate (**11**)[7] with primary amines. However, instead of the desired displacement of the methoxyl group, the only reaction that was observed with aniline or benzylamine was nucleophilic displacement at a methyl group on the quaternary nitrogen to give the hydrazinic ester **12**. The structure of **12** was established by reconversion to **11** by reaction with methyl tosylate.



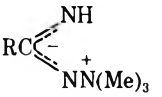
11 12

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. NMR spectra were determined on a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as an internal standard.

1,1,1-Trimethyl-2-(*N*-phenylbenzimidoyl)hydrazinium Hydroxide Inner Salt (4). A solution of KO-*t*-Bu was prepared from 4.0 g (0.1 mol) of potassium in 100 mL of dry *t*-BuOH. The solution was evaporated with a rotary evaporator and the residue heated at 100 °C at reduced pressure for 30 min. The resulting KO-*t*-Bu (containing *t*-BuOH) and 11.2 g (0.1 mol) of 1,1,1-trimethylhydrazinium chloride[8] were suspended in 150 mL of dry THF and vigorously stirred in a nitrogen atmosphere for 3 days. The suspension was rapidly filtered to remove KCl and transferred to a 500-mL three-necked flask equipped with a pressure-equalizing dropping funnel, nitrogen inlet tube, and magnetic stirrer. A solution of 10.5 g (0.05 mol) of *N*-phenylbenzimidoyl chloride[9] in 20 mL of anhydrous THF was added from the dropping funnel to the stirred, ice-cooled solution. Stirring was continued for 2 h at 0 °C. Filtration afforded a solid mixture (11.3 g) consisting of 1,1,1-trimethylhydrazinium chloride and the ylide. The ylide was separated from the salt by extraction with hot benzene and was precipitated with petroleum ether to give 5.90 g of product, mp 172–175 °C. An additional 3.3 g (mp 162–165 °C) was obtained

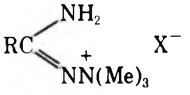
Table I. Ylides (3)



Compd	Formula	$(CH_3)_3\overset{+}{N}NH_2$ employed	Reaction time, h	Crude yield, %	Mp, °C	NMR ($CDCl_3$), δ
3a	$C_5H_{13}N_3$	Chloride	6	58	107–116[a]	3.45 (s, 9 H), 1.78 (s, 3 H), 7.48 (s, 1 H)
3a		Tosylate	6	86	105–117	
3b	$C_6H_{15}N_3$	Tosylate	6	67	83–93	3.45 (s, 9 H), 1.05 (t, 3 H, J = 9 Hz), 1.98 (q, 2 H, J = 9 Hz), 7.30 (s, 1 H)
3c	$C_{10}H_{15}N_3$	Chloride	15	66	140–141[b]	3.42 (s, 9 H), 7.1–7.5 (m, 6 H)
3c		Tosylate	14	70	138–141	
3d	$C_{10}H_{14}ClN_3$	Tosylate	23	62	Oil	3.54 (s), 7.1–7.6[c] (m)
3e	$C_{11}H_{17}N_3O$	Tosylate	6	48	Oil	3.45 (s, 9 H), 3.68 (s, 3 H), 6.6–7.6[d] (m)
3f	$C_9H_{14}N_4$	Tosylate	12	49[e]	117–120	3.53 (s, 9 H), 7.0–8.8 (m, 4 H), 5.1 (broad, 1 H)

[a] Reported[4] mp 124 °C. [b] Anal. Calcd for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53. Found: C, 67.34; H, 8.43. [c] The spectrum indicated contamination with a small quantity of benzene. Aromatic AB at δ 7.15 and 7.49 (J = 9 Hz). [d] Contaminated with a small quantity of benzene. Aromatic AB at δ 6.72 and 7.50 (J = 9 Hz). [e] Yield of hygroscopic solid after recrystallization from acetone.

Table II. Ylide Salts



Compd	Mp, °C	Recrystn solvent	Formula	Calcd C	Calcd H	Found C	Found H
3a picrate	140–141[a]	EtOH	$C_{11}H_{16}N_6O_7$				
3a HCl	235–237	EtOH	$C_5H_{14}ClN_3$	39.60	9.30	39.47	9.20
3a HI	187–188	EtOH	$C_5H_{14}IN_3$	24.70	5.80	24.68	5.86
3b picrate	149–151	EtOH	$C_{12}H_{18}N_6O_7$	40.33	4.79	40.21	5.00
3c HCl	237–238	MeOH–ether	$C_{10}H_{16}ClN_3$	56.26	7.56	56.20	7.55
3c HI	212–213	EtOH	$C_{10}H_{16}IN_3$	39.36	5.29	39.27	5.40
3d picrate	220–222	DMF	$C_{16}H_{17}ClN_6O_7$	43.49	4.11	43.80	3.89
3e picrate	216–218	DMF	$C_{17}H_{20}N_6O_8$	46.78	4.61	46.73	4.42
3f dipicrate	227–228	DMF–EtOH	$C_{21}H_{20}N_{10}O_{14}$	39.67	3.01	39.58	3.06

[a] Reported[4] mp 144 °C.

by extraction of the residue remaining after evaporation of the THF filtrate with 50 mL of boiling benzene followed by precipitation with petroleum ether. The combined yield of crude ylide obtained by this procedure was 72%.

The analytical sample was obtained as white crystals, mp 174–175 °C dec, by recrystallization from benzene.

Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.81; H, 7.84; N, 16.28.

Spectroscopic data and other properties of this compound have been previously reported.[1]

General Procedure for Preparation of Ylides (3). The nitrile (25 mmol) and 25 mmol of 1,1,1-trimethylhydrazinium chloride (or tosylate[6a]) were added to 40 mL of dry *t*-BuOH containing 25 mmol of KO-*t*-Bu (prepared from potassium). The reaction mixtures were heated and stirred for the times indicated in Table I. The solvent was removed in vacuo and the ylides were extracted from the inorganic material with several portions of boiling benzene. Evaporation of the combined extracts afforded the crude, hygroscopic products.

Alkylation of 1,1,1-Trimethyl-2-acetimidoylhydrazinium Hydroxide Inner Salt (3a). A. Methyl Iodide. Methyl iodide (15 mL) was cautiously added through a reflux condenser to a stirred solution containing 15 g (0.13 mol) of the ylide in 75 mL of dry acetonitrile. After the exothermic reaction had subsided, the reaction mixture was cooled and the product (**6a** HI) was filtered off as white crystals (21.5 g), mp 215–216 °C. Recrystallization from ethanol did not alter the melting point. NMR (Me_2SO-d_6) δ 3.32 (s, 9), 2.20 (s, 3), 2.50 (s, 3), 7.30 (broad NH, 1). When determined in D_2O, the NMR spectrum of **6a** HI displayed two sets of signals: δ 3.50, 3.52 [s, $(CH_3)_3N^+$], 2.08, 2.38, (s, CH_3C, rel intensity 1:1.7), 3.02, 2.72 (s, CH_3N, rel intensity 1:1.7). The intensities of these signals were found to be time independent. On heating the D_2O solution, the signals showed no tendency to coalesce, but at 70 °C, their intensities became equivalent.[10]

Anal. Calcd for $C_6H_{16}N_3I$: C, 28.03; H, 6.27. Found: C, 27.97; H, 6.16.

Attempted alkylation of **3a** with methyl iodide in refluxing ethanol afforded a 62% yield of **3a** HI and no detectable methylation.

The iodide (**6a** HI) (1.9 g), 0.55 g of sodium methoxide, and 50 mL of dry acetonitrile were heated under reflux and stirred for 3 h. The solvent was removed in vacuo and crude **1,1,1-trimethyl-2-(*N*-methylacetimidoyl)hydrazinium hydroxide inner salt (6a)** was separated from the solid residue by several extractions with boiling benzene. Evaporation afforded a quantitative yield of the ylide as a hygroscopic solid that was purified by vacuum sublimation as extremely hygroscopic white crystals: mp 67–71 °C; NMR (Me_2SO-d_6) δ 3.38 (s, 9), 1.50 (s, 3), 2.78 (s, 3).

Anal. Calcd for $C_6H_{15}N_3$ (anhydrous): C, 56.77; H, 11.70; N, 32.52. Calcd for $C_6H_{15}N_3$ containing 6.27% H_2O (calculated from oxygen content by difference): C, 52.28; H, 11.66; N, 30.45. Found: C, 52.30; H, 11.75; N, 30.38.

B. Ethyl Iodide. The ylide (2.7 g) was added to 4.5 mL of ethyl iodide. After briefly warming the solution on the steam bath, an exothermic reaction ensued and the reaction mixture solidified. The crude salt was filtered and washed with ether. Recrystallization from ethanol–ether gave 4.85 g (78%) of **6b** HI, mp 185–190 °C. The analytical sample was prepared by recrystallization from ethanol as white crystals: mp 193–194 °C, NMR (D_2O) δ 3.40 [s, 9 $(Me)_3N^+$], 0.85–1.19 (superimposed triplets, 3, CH_2CH_3), 1.88 and 2.15 [s (rel intensities 1:1.4), 3, CCH_3], 3.1 (m, 2, CH_2CH_3), NMR (Me_2SO-d_6) δ 3.41 [s, 9 $(Me)_3N^+$], 0.85–1.15 (superimposed triplets, 3, CH_2CH_3), 2.9 (m, 2 CH_2CH_3).[10]

Anal. Calcd for $C_7H_{18}IN_3$: C, 31.01; H, 6.69; N, 15.50. Found: C, 30.76; H, 6.42; N, 15.46.

Neutralization of the iodide by the procedure described above for **6a** HI gave 1,1,1-trimethyl-2-(*N*-ethylacetimidoyl)hydrazinium hydroxide inner salt (**6b**) as a hygroscopic oil: bp 81–91 °C (2.5 mm);

distilled yield 66%; NMR (neat) δ 3.24 (s, 9), 2.85 (q, 2, J = 7 Hz), 2.37 (s, 3), 0.85 (t, 3, J = 7 Hz).

Anal. Calcd for $C_7H_{17}N_3$ (anhydrous): C, 58.7; H, 12.0; N, 29.3. Calcd for $C_7H_{17}N_3$ containing 2.7% H_2O (calculated from oxygen content by difference): C, 57.1; H, 12.0; N, 28.5. Found: C, 57.2; H, 11.9; N, 28.5.

Acetamide Dimethylhydrazone (8). The hydriodide of this compound was prepared by reaction of S-methylthioacetamidium iodide[11] utilizing the procedure of Reynaud and co-workers.[12] The solution resulting from neutralization of the crude hydriodide with 2 N NaOH was saturated with Na_2SO_4 and extracted with several portions of chloroform. The dried chloroform extracts, on evaporation, gave the crude amidrazone in 82% yield, mp 71–76 °C (lit. mp[13] 79–80 °C).

Acetimidic Acid Trimethylhydrazide Hydriodide (9). Reaction of 2.12 g of **8** with 4.2 mL of methyl iodide resulted in an exothermic reaction. The crude solid was washed with ether and recrystallized from ethanol–ether to give 2.15 g of the iodide, mp 143–149 °C. The analytical sample was obtained by recrystallization from ethanol as white crystals: mp 154–156 °C; NMR (Me_2SO-d_6) δ 3.11 (s, 3), 2.48 (s, 6), 2.30 (s, 3), 8.8 (broad NH, exchangeable, 2).

Anal. Calcd for $C_5H_{14}IN_3$: C, 24.70; H, 5.80; N, 17.29. Found: C, 24.71; H, 5.53; N, 17.61.

The iodide was neutralized with 1 equiv of sodium methoxide in methanol. The free base (**10**) was obtained by benzene extraction of the residue remaining after removal of the solvent. Evaporation of the dried benzene extracts gave **10** as a dark oil: IR 1610 cm^{-1} (=NH); NMR ($CDCl_3$) δ 2.01 (s, 3), 2.36 (s, 6), 2.78 (s, 3), 5.49 (s, 1, NH). The base underwent extensive decomposition on attempted vacuum distillation.

Crude **10** (0.8 g), 5 mL of 6 N NaOH, and 5 mL of ethanol were heated under reflux for 1.5 h. The solution was concentrated to half volume, saturated with NaCl, and extracted with chloroform. Evaporation of the dried extracts gave 0.5 g of oily 1,1,2-trimethyl-2-acetylhydrazine which was identical (IR and NMR) with an authentic sample.[14]

Reaction of Benzamide Dimethylhydrazone (7) with Methyl Iodide. The amidrazone[12] (1.0 g) was treated with 2 mL of methyl iodide. After 24 h at room temperature, the solid product was filtered and washed with ether. Recrystallization from ethanol gave 0.34 g (19%) of **1,1,1-trimethyl-α-aminobenzylidenehydrazinium iodide (3c HI)**, mp 200–204 °C. The product was indentical (NMR, IR) with that obtained by reaction of hydriodic acid with **3a** (Table II). Evaporation of the filtrate afforded a syrupy mixture that could not be separated and displayed a complex NMR spectrum.

1,1-Dimethyl-2-α-methoxybenzylidenehydrazine (12). Benzylamine (10 mL) and 5.0 g of 1,1,1-trimethyl-α-methoxybenzylidenehydrazinium tosylate[7] (**11**) were heated at 170 °C for 2.5 h. The reaction mixture was diluted with ether to give 3.8 g of benzylammonium tosylate (by IR). The ether was evaporated and the residue dissolved in chloroform and extracted with four 20-mL portions of 3 N HCl. The acid extracts were saturated with salt and extracted with several portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to give 1.2 g (50%) of crude **12** as a semisolid. Kugelrohr distillation (120 °C, 0.50 mm) gave white crystals: mp 83–85 °C; NMR ($CDCl_3$) δ 2.34 (s, 6), 2.89 (s, 3), 6.9–7.6 (m, 5).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.35; H, 7.91; N, 15.71. Found: C, 67.50; H, 7.91; N, 15.72.

Reaction of **11** with aniline at 175 °C gave low yields (<10%) of **12**.

Reconversion of **12** to **11** was accomplished by heating 0.3 g of **12** with 0.31 g of methyl tosylate at 120 °C for 4.5 h. Recrystallization of the ether-insoluble material from chloroform–ethyl acetate gave 0.11 g of **11**, mp 123–125 °C.

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Registry No.—**3a,** 13848-75-4; **3a** picrate, 13833-34-6; **3a** HCl, 61787-76-6; **3a** HI, 61787-77-7; **3b,** 61787-74-4; **3b** picrate, 61787-79-9; **3c,** 61787-75-5; **3c** HCl, 61787-80-2; **3c** HI, 61787-81-3; **3d,** 61787-82-4; **3d** picrate, 61827-41-6; **3e,** 61787-83-5; **3e** picrate, 61787-85-7; **3f,** 61787-86-8; **3f** dipicrate, 61787-89-1; **4,** 51283-81-9; **6a,** 61787-90-4; **6a** HI, 61787-91-5; **6b,** 61787-92-6; **6b** HI, 61787-93-7; **7,** 38706-49-9; **8,** 25430-77-7; **9,** 61787-94-8; **10,** 61787-95-9; **11,** 58426-21-4; **12,** 61787-96-0; acetonitrile, 75-05-8; propionitrile, 107-12-0; benzonitrile, 100-47-0; 4-chlorobenzonitrile, 623-03-0; 4-methoxybenzonitrile, 874-90-8; 3-pyridinecarbonitrile, 100-54-9; 1,1,1-trimethylhydrazinium chloride, 5675-48-9; N-phenylbenzimidoyl chloride, 4903-36-0; 1,1,1-trimethylhydrazinium tosylate 27808-77-1; methyl iodide, 74-88-4; ethyl iodide, 75-03-6.

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2,5-Dihydro-3-azido-5-oxo-1,2,4-triazines and Related Compounds. Syntheses and Structure Elucidation

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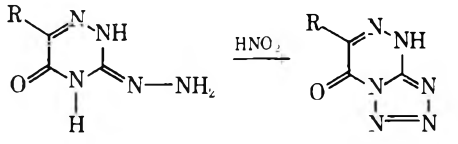
Several 3-azido-2,5-dihydro-5-oxo-1,2,4-triazines were prepared by treating the corresponding 3-hydrazino derivatives with nitrous acid. The azidotriazines spontaneously cyclized into a tetrazolo isomer. These transformations were studied using nuclear magnetic resonance and infrared spectroscopic methods. The tetrazolo isomers which could cyclize either into the N-2 or N-4 positions were proven to be tetrazolo[1,5-*b*]-2,5-dihydro-5-oxo-1,2,4-triazines by a ^{13}C NMR spectroscopic study.

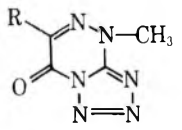
Dornow, Menzel, and Marx[1,2] have reported the oxidation of some 6-substituted 3-hydrazino-2,5-dihydro-1,2,4-triazines, which they considered as having structure **1**, with nitrous acid. Without an unequivocal structure proof, they assigned the tetrazolo[1,5-c]-1,2,4-triazine structure **2** (**a** and **b**) to these oxidation products.



1 **2a, b**

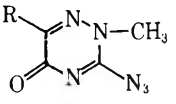
a, R = CH_3
b, R = C_6H_5

Treatment of one of the oxidation products (**2a**) with diazomethane afforded an *N*-methyl derivative which was stated to be isomeric with compound **3a**. The open-chain isomer **4a** was not considered as a possibility.



3

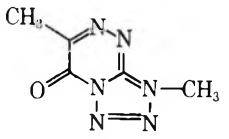
a, R = CH_3
b, R = H



4

a, R = CH_3
b, R = H

These authors suggested that the diazomethane reaction product might conceivably have structure **5** or **6**.



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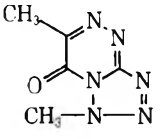

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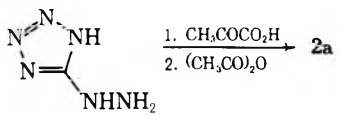
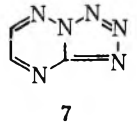
Further proof in support of structure **2a**, the initial cyclization product, was offered based upon the following interconversion:



In view of the fact that we have shown that 3-azido-1,2,4-triazines cyclize spontaneously to form tetrazolo[1,5-*b*]-1,2,4-triazines (**7**) rather than the isomeric compounds of type



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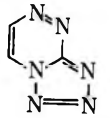
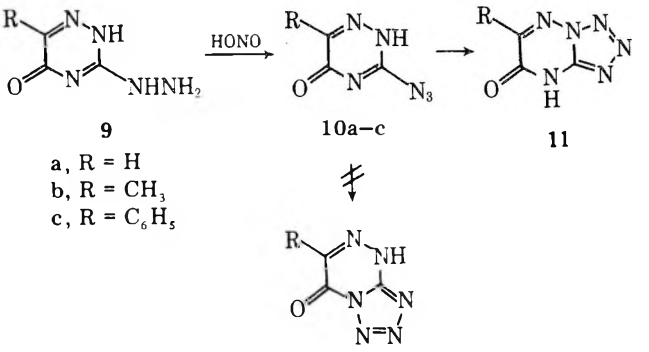


8

8,[3] we decided to reexamine the structures proposed by Dornow, Menzel, and Marx.

Our synthetic approach involved the nitrous acid oxidation of 3-hydrazino-2,5-dihydro-5-oxo-1,2,4-triazines (**9a–c**) (cf. Scheme I). The initial product of the oxidation, the azido

Scheme I



9 **10a–c** **11**

a, R = H
b, R = CH_3
c, R = C_6H_5

2

compounds **10a–c**, can, in principle, cyclize to form either compounds of general structure **2** or **11a–c**.

The infrared spectrum of the oxidation product of **9a** obtained either in the solid state or in chloroform solution showed the presence of absorption due to the azido group (2160–2120 cm^{-1}), as well as absorption due to the presence of a tetrazolo ring (1100–1000 cm^{-1}) (cf. Table I). The azido asorption is time dependent in solution and disappears within 2 h at room temperature. On the other hand, oxidation of the 6-methyl (**9b**) and the 6-phenyl (**9c**) derivatives affords only one product, devoid of any azido absorption in the solid state (the compounds are insoluble in chloroform). It now remains to establish whether cyclization of the azido compounds (**10a–c**) occurs to form the tetrazolo derivatives **2** or **11**.

We had selected to compare the ^1H NMR spectra of the triazolo derivatives **12a** and **13a**[4] (in dimethyl sulfoxide) with the ^1H NMR spectrum of the oxidation product of the hydrazino-1,2,4-triazine **9a**. Unfortunately, the chemical shift difference of the six-membered ring proton between **12a** and **13a** is insignificant and thus no comparisons could be made. Thus, we took recourse to an analysis of the ^{13}C NMR spectra of some of these compounds (cf. Table III).

In order to identify the absorptions due to C-3 and C-6 in compound **12a**, we obtained the ^{13}C spectrum of its 6-methyl derivative (**12b**). It is well known that replacement of a proton by a methyl group on a sp^2 carbon causes the latter to become more deshielded by approximately 9 ppm.[5] Consequently, the shift of the 145.0-ppm peak in compound **12a** to 154.0 ppm in its 6-methyl derivative (**12b**) identifies this peak as being due to C-6. The remaining resonance peaks are, as expected, not significantly affected in going from the "parent" com-

Table I. Infrared Absorption Spectra (cm^{-1}) of Some Substituted 1,2,4-Triazines

Compd	"Phase"	C=O	C=N	Azido bands	Tetrazolo bands
3a	Nujol	1720	1604, 1534		1090, 1068, 992, 978
	$CHCl_3$	1670		2170, 2180	
3b	Nujol	1728	1600, 1515		1090, 1068, 982, 968
	$CHCl_3$	1660		2170	
11a	Nujol	1702	1620, 1554	2170, 2130	1080, 1060, 970, 950
	$CHCl_3$	1702	1615, 1550		1085, 1060, 964, 948
11b	Nujol	1700	1630, 1570		1080, 1060, 960
11c	Nujol	1700	1638, 1570		1085, 1060, 970, 950
15a	Nujol	1700	1625, 1570		1090, 1040, 985, 965
15b	Nujol	1695	1620, 1570		1105, 1060, 978, 965
15c	Nujol	1700	1620, 1552		1100, 1060, 960
	$CHCl_3$	1700	1615, 1545		
10a	Nujol			2170, 2180	
	$CHCl_3$			2170, 2180	

Table II. ^1H NMR Spectra (δ ppm) of Some 1,2,4-Triazines

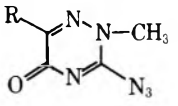
Compd	Solvent[a]	R_1	R_2	R_3	R_4	R_5	R_6	R_8
3a	Me_2SO-d_6				4.02		2.33	
3a	$CDCl_3$				4.15		2.51	
3b	$CDCl_3$				4.24		7.27	
3b	Me_2SO-d_6				4.09		9.01	
4a	$CDCl_3$		3.77				2.27	
4b	$CDCl_3$		3.70				7.58	
10c	Me_2SO-d_6						7.99	
11a	Me_2SO-d_6						8.22	
	Acetone-d_6						8.12	
11b	Me_2SO-d_6						2.36	
11c	Me_2SO-d_6						9.03–9.20 (m)	
							8.60–8.72	
12a	Me_2SO-d_6			9.10			7.89	
12b	Me_2SO-d_6			9.03			2.27	
13a	Me_2SO-d_6		8.40				7.87	
13b	Me_2SO-d_6		8.37				2.37	
14	$CDCl_3$	9.85			4.15		2.50	
15a	Me_2SO-d_6						2.37	3.52
15b	Me_2SO-d_6						9.03–9.20 (m)	3.63
							8.60–8.72	
15c	Acetone-d_6						8.18	4.63
	$CDCl_3$						8.48	4.28

[a] Dilute solutions in indicated solvents. A Varian HA-100 NMR spectrometer was used to obtain these spectra.

pound **12a** to its 6-methyl derivative (**12b**).[2] Since the bridgehead carbon is expected to have the longest relaxation time (lowest intensity peak) and remains a singlet in the coupled ^{13}C spectrum it is readily identified as having a chemical shift of 144 ppm. The oxygen bearing carbon will be the most deshielded one in the ring system (155.8 ppm) and is identifiable on that basis. Similar reasoning can be used to assign the ^{13}C peaks in compounds **13a** and **13b**.[4] These arguments can now be employed to unequivocally differentiate between structures **2** and **11**. Clearly, the ^{13}C resonances [^{13}C δ (ppm) 144, 145, 152] of the tetrazolotriazine are consistent with the N-2 cyclized structure **11** when compared to its "deaza" N-2 cyclized analogue **12a** [^{13}C δ (ppm) 145, 144, 156] rather than with the N-4 cyclized compound **13a** [^{13}C δ (ppm) 131, 148, 151].

Thus, as is the case in the 3-azido-1,2,4-triazines, cyclization occurs onto N-2 in these compounds as well. The one unique feature of this ring system as compared to the nonoxo form **7** lies in the observation that the initial azido form of these compounds has finite stability (2 h) even in dimethyl sulfoxide (cf. Table II).

The propensity toward cyclization of the 3-azido-1,2,4-triazines into N-2 rather than N-4 prompted us to examine the derivative **4a,b**, where cyclization into N-2 is impossible:



4

a, R = CH_3
b, R = H

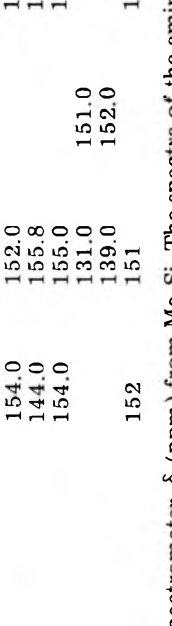
These compounds were prepared from the known 2-methyl-3-methylthio-2,5-dihydro-5-oxo-1,2,4-triazines by converting them successively to the 3-hydrazino derivatives and oxidation of the latter to compounds **3a,b** or **4a,b**. The infrared spectrum of the oxidation products obtained in the solid state did not show any absorption in the azido group region. Thus, the compounds exist, in the solid state at least, as the tetrazolo derivative **3a,b**.

However, the ^1H NMR spectrum of a solution of compound **3a** in deuteriochloroform shows the presence of two species in the ratio of 2:1. In order to establish which set of peaks (δ 2.27, 3.77 or 2.51, 4.15) corresponds to the open (**4a**) and which to the closed (**3a**) form, recourse was taken to a spectral comparison with compound **14**.

Clearly, the lower intensity set of peaks (δ 4.15, 2.51) correspond to the N-4 cyclized isomer **3a**, while the high-intensity peaks (δ 2.27 and 3.77) correspond to the open-chain form **4a**. In fact, a comparison of the ^{13}C chemical shifts of **3b** with

Table III. ^{13}C NMR Spectra (Chemical Shifts in δ, ppm)[a]

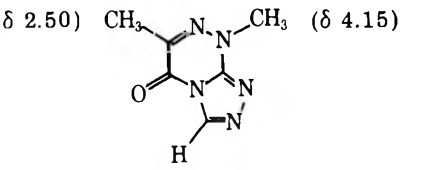
X = CH, N



X = CH, N

Compd	Solvent	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	R_2	R_5	R_6	R_7	R_8
3a	$CDCl_3$			147.0			141	154.5			42.0		16.5	
3b	Me_2SO-d_6			145.5			131.0	149.0			41.5			
4a	$CDCl_3$		150.5			151.0						17.0		
					161.5					41.0				
11a	Me_2SO-d_6					145.0	152.0		144.0					
11b	Me_2SO-d_6					154.0	152.0		144.0			18.0		
12a	Me_2SO-d_6		134.0			144.0	155.8		145.0					
12b	Me_2SO-d_6		135.0			154.0	155.0		144.5			18.0		
13a	Me_2SO-d_6	149.0		148.0			131.0	151.0					17.5	
13b	Me_2SO-d_6	148.5		148.0			139.0	152.0						30
15c	Me_2SO-d_6					152	151		145			18		

[a] ^{13}C spectra were taken with a Hitachi Perkin-Elmer R-26 spectrometer, δ (ppm) from Me_4Si. The spectra of the amino compounds were obtained as 1.5 M solutions in Me_2SO-d_6; all of the others were obtained as 1.5 M solutions in $CDCl_3$. The pulse intervals were 16 s, and a pulse angle of 50° with a total of about 500 scans per spectrum. All spectra were wide-band proton decoupled.



14

those of compound **13a** conclusively prove the mode of cyclization (cf. Table III). These data also unequivocally establish that in the absence of an *N*-methyl group on N-2, cyclization does indeed take place at that position. This equilibrium in $CDCl_3$ is shifted slightly in greater favor of the azido form, when a hydrogen is present at C-6, when the ratio becomes 2.1:1. Interestingly, the ^1H NMR spectra of these compounds in dimethyl sulfoxide show the presence of *only* the closed species.

Conclusions

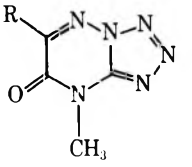
This study has established the following facts:

1. 3-Azido-5-oxo-2,5-dihydro-1,2,4-triazines in dimethyl sulfoxide or deuteriochloroform exist as the N-2 cyclized isomers (**11**).

2. The presence of a 5-oxo group in the 1,2,4-triazines does not alter the direction of cyclization.

3. The structure assigned to these oxidation products (**2a,b**) by others is incorrect.

4. The N-methylation product assigned either structure **5** or **6** is, in fact, the N-4 methylated compound (**15a**).



15

a, R = CH_3
b, R = C_6H_5
c, R = H

5. When N-2 in 3-azido-5-oxo-2,5-dihydro-1,2,4-triazines is N-methylated, an equilibrium exists between the azido (**4**) and the N-4 cyclized tetrazolo isomers (**3**).

Experimental Section[6]

7,8-Dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (11). To a 25-mL Erlenmeyer flask was added 2,5-dihydro-5-oxo-3-hydrazino-1,2,4-triazine (254 mg, 2 mmol) and 5 N HCl (6 mL). The solution was cooled to 0–5 °C and aqueous $NaNO_2$ (140 mg in 1 mL of H_2O) was added dropwise. The solution was stirred for an additional 1 h while maintaining the temperature at 0–5 °C. The crude tetrazole was separated by extraction with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$ extracts were evaporated to dryness and the residue recrystallized from absolute methanol to afford 7,8-dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (**11a**) (114 mg, 39%, mp 170–172 °C, mass spectrum mol wt 138).

7,8-Dihydro-8-methyl-7-oxotetrazolo[1,5-*b*]-1,2,4-triazines (15) (General Procedure). A solution of the appropriate 7,8-dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (3 mmol), dimethyl sulfoxide (5 mL), anhydrous K_2CO_3 (0.5 g), and CH_3I (0.57 g, 4 mmol) was stirred at room temperature for 24 h. The Me_2SO was removed by distillation (90 °C, 0.3 mm) to afford a dark brown residue. The residue was washed with water, filtered, and recrystallized from absolute ethanol (**15a**, mp 210–212 °C, 36%; **b**, 199–200 °C, 73%, **c**, 153–155 °C, 31%).

4,7-Dihydro-4-methyl-7-oxotetrazolo[5,1-*c*]-1,2,4-triazine (3b). A solution of 2,5-dihydro-2-methyl-3-hydrazino-5-oxo-1,2,4-triazine (423 mg, 3 mmol) and 5 N HCl (9 mL) was cooled to 0–5 °C and aqueous $NaNO_2$ (207 mg) in 2 mL of H_2O was added dropwise. The solution was stirred for an additional 30 min while maintaining the temperature at 0–5 °C. The solution was extracted with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$ extracts were evaporated to dryness and the residue was sublimed (110 °C, 0.5 mm) to afford 4,7-dihydro-4-methyl-7-oxotetrazolo[5,1-*c*]-1,2,4-triazine (0.29 g, 64%, mp 150–151 °C, mass spectrum mol wt 152).

Registry No.—**3a**, 61788-10-1; **3b**, 61788-11-2; **4a**, 61788-12-3; **4b**, 61788-13-4; **9a**, 21383-22-2; **9b**, 38736-23-1; **9c**, 61788-14-5; **10a**, 61788-15-6; **10c**, 61788-16-7; **11a**, 61788-17-8; **11b**, 61788-18-9; **11c**, 61788-19-0; **12a**, 874-40-8; **12b**, 19542-10-0; **13a**, 57351-74-3; **13b**, 57250-39-2; **14**, 25623-69-2; **15a**, 61788-20-3; **15b**, 61788-21-4; **15c**, 61788-22-5; 2,5-dihydro-2-methyl-3-hydrazino-5-oxo-1,2,4-triazine, 39214-97-6.

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(6) Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument on all new compounds. Their molecular ions and fragmentation patterns are consistent with the indicated structures. A Varian HA-100 instrument was used to record the ^{1}H NMR spectra. Melting points are corrected. Elemental analyses on all new compounds were performed by Atlantic Microlab. Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama, and are within the accepted standards for C, H, and N analyses.

Selective N-Oxidations of Chlorinated Pyrazines and Quinoxalines

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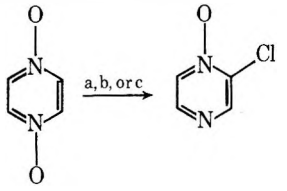
Chlorinated pyrazines and quinoxalines are specifically oxidized on the nitrogen adjacent to the halogen-bearing carbon by means of Caro's acid (peroxysulfuric acid) in concentrated sulfuric acid. This procedure affords the first simple, direct, and high-yield synthesis of 2-chloropyrazine 1-oxides. The use of lanthanide induced shift (LIS) reagents to unambiguously identify isomers was complicated by the presence of two nonequivalent coordination sites. The role of the strong-acid reaction medium in determining the steric course of oxidation is discussed.

Aromatic diazines in which the basicity of the ring nitrogens is severely reduced by electron-withdrawing substituents such as halogens are often resistant to N-oxidation by the usual peroxycarboxylic acid reagents.[2-4] The peracetic acid oxidations of chloropyrazines and chloroquinoxalines occur in such a manner that the most basic and least hindered nitrogen atom is oxidized exclusively.[2-5] In other words, N-oxidation of a pyrazine bearing a halogen substituent takes place on the nitrogen farthest removed from that substituent, e.g., 2-chloropyrazine → 2-chloropyrazine 4-oxide. Several 2-chloro 1-oxide isomers of pyrazine and quinoxaline have been prepared, but generally in low yield and indirectly from the bis *N*-oxide (eq 1).[6-11] Furthermore, dihalogenated py-



(1)

a, $POCl_3$
b, aq HCl, $h\nu$
c, $C_6H_5SO_2Cl$ or $SOCl_2$

razines are notoriously difficult to oxidize; 2,6-dichloropyrazine 4-oxide is obtained in only 4% yield by direct oxidation.[12]

Quite recently, several new oxidizing systems (peroxydichloromaleic acid,[13] CF_3CO_2H–H_2SO_4–90% H_2O_2,[14] and H_2SO_4–60% H_2O_2[15]) have been found to effect the oxidation of polyhalogenated diazines. The success of these novel reagents prompted us to extend the application of one of them to mono- and dichlorinated pyrazines and quinoxalines.

In terms of simplicity, cost, and availability of reagents, the oxidation procedure of Kyriacou appeared to be the method of choice for large-scale applications.[15] The handling of 60–90% hydrogen peroxide, however, presented serious safety implications. The conditions employed in such strong-acid oxidations, viz., sulfuric acid and hydrogen peroxide, suggest that the actual oxidizing agent is Caro's acid (peroxysulfuric acid). This being the case, this same intermediate could be generated from potassium persulfate and sulfuric acid, thus avoiding the use of potentially hazardous concentrated peroxide. Duplication of the previously reported oxidations of tetrachloropyrazine, substituting persulfate for peroxide, verified this hypothesis.

With a modified procedure which consisted of dissolving the halogenated diazine in sulfuric acid and of slowly adding potassium persulfate at 10 °C, a series of chlorinated pyrazines and quinoxalines were successfully converted to their *N*-oxides in high yield (see Experimental Section). Somewhat unexpectedly, however, the monochloropyrazines afforded the 2-chloro 1-oxide isomers in high purity. To verify the structural assignments of these derivatives, the 2-chloro 4-oxide isomers were prepared by known routes for comparison of physical and spectral properties. With the exception of the *N*-oxide isomers of 2,6-dichloropyrazine, all isomers could be distinguished by well-separated melting points. 2,6-Dichloropyrazine 1-oxide (mp 122–123.5 °C) and 2,6-dichloropyrazine 4-oxide (mp 119–121 °C) gave a typical mixture melting point depression (mp 85–90 °C).

The IR and NMR spectra of each pair of isomers are substantially different. All of the *N*-oxides display an N–O stretching frequency in the region of 1350–1260 cm^{-1}, but isomer identification by this method (1-oxides exhibit a deviation to lower frequencies than the corresponding 4-oxides)[8,9] was deemed tenuous because more than one substituent was present in most cases. The NMR spectra, however, are more informative (see Table I). Based on an examination of these data and on the shielding effects of the *N*-oxide function,[9] the following corollary can be formulated: *a given ring proton will generally resonate at higher field in 2-chloropyrazine 4-oxides than in the corresponding 1-oxide isomers.* While this criterion is useful in distinguishing between a pair of isomers, its utility is limited in that both isomers should be available for direct comparison.

In an attempt to develop a method to unambiguously identify a single isomer, the effects of lanthanide induced

Table I. Chemical Shift Data for Heteroaromatic Protons of Chloropyrazines and Chloroquinoxalines and Their *N*-Oxides

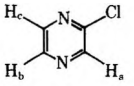
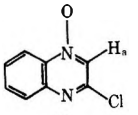
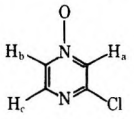
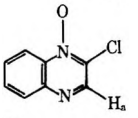
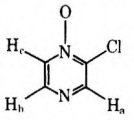
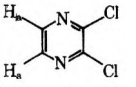
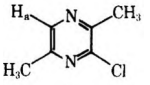
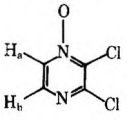
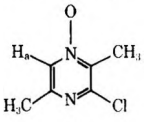
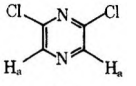
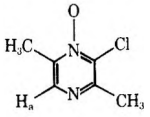
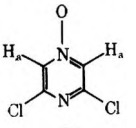
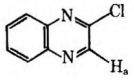
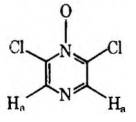
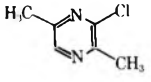
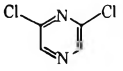
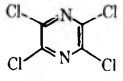
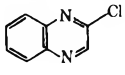
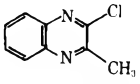
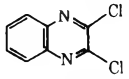
Registry no.	Compd		δ, ppm	Registry no.	Compd		δ, ppm
14508-49-7	I		a 8.70 b 8.46 c 8.63	5227-59-8	XIII 	a	8.38
6863-76-9	II		a 8.12 b 7.96 c 8.22	5227-57-6	XIV 	a	8.75
16025-16-4	III		a 8.62 b 8.36 c 8.22	4858-85-9	VII 	a	8.40
95-58-9	IV		a 8.20	61689-43-8	VIII 	a + b	8.15
61689-41-6	V		a 8.20	4774-14-5	IX 	a	8.60
61689-42-7	VI		a 8.48	14399-36-1	X 	a	8.02
1448-87-9	XII		a 8.75	61655-70-7	XI 	a	8.50

Table II. Direct Oxidation of Halogenated Pyrazines and Quinoxalines

Substrate	Registry no.	Method	Product[25]	Registry no.	% yield	Mp, °C
		a b	1-Oxide 4-Oxide		55 22	131–132 (lit.[9] 133–134) 94–95 (lit.[5] 95–96)
		a b	1-Oxide 4-Oxide		40 42	105–109 (lit.[7] 106–109) 110–112 (lit.[7] 116–117)
		a b	1-Oxide 4-Oxide		62 1.2	122–123 119–121 (lit.[12] 123–125)
		a b	1-Oxide		85 0	104–106
	13484-50-9	a c	1-Oxide 1,4-Dioxide	27338-53-0 32051-15-3	65 70	216–218 (lit.[26] 216–218) 315 (lit.[15] 310)
		a b	1-Oxide 4-Oxide		52 6	110–112 (lit.[10,11] 114) 150–152 (lit.[10] 152–153)
	32601-86-8	a b	1-Oxide 4-Oxide	61689-44-9 61689-45-0	32 31	105–106 89–91
	2213-63-0	a b	1-Oxide	53870-24-9	80 0	138–139 (lit.[11] 138–139)

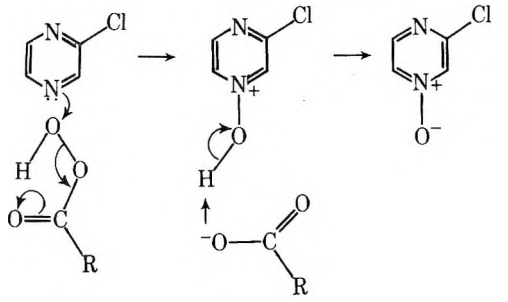
[a] H_2SO_4–$K_2S_2O_8$. [b] HOAc–30% H_2O_2. [c] 2 equiv of $K_2S_2O_8$–H_2SO_4.

shifts (LIS) on the NMR spectra of chlorinated pyrazine *N*-oxides were qualitatively examined. The site of coordination between such difunctional substrates and a shift reagent depends upon the basicity of the individual groups.[16–18] Both the oxygen of the *N*-oxide and heterocyclic nitrogen can effectively coordinate with lanthanide shift reagents,[17,18] and only one example of both functionalities in the same molecule has been reported.[19] From Rondeau's work,[19] one might expect the *N*-oxide to be the preferential site of coordination. However, steric conditions in the vicinity of the basic center are an equally important factor.[16] The LIS for a series of isomeric pyrazine and quinoxaline *N*-oxides with europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione) indicate that coordination at only one site is inconsistent with

the observed behavior.[20] Although positive isomer identification is unfeasible, LIS proved most useful for resolving the accidental degeneracy of the ring protons in 2,3-dichloropyrazine 1-oxide.

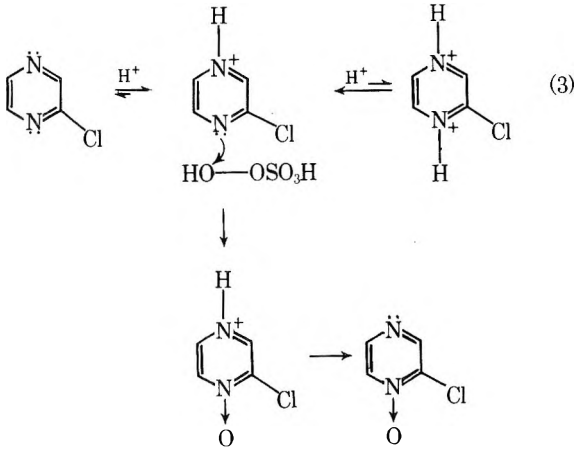
With the course of the reaction verified, the scope of the persulfate oxidation was investigated. In general, the oxidation terminates at the mono *N*-oxide stage regardless of the amount of oxidizing agent employed. The attempted oxidation of 2-chloropyrazine 4-oxide under similar conditions also fails to give any bis *N*-oxide. Only in the case of tetrachloropyrazine is the bis *N*-oxide obtained. Furthermore, the persulfate oxidation method is apparently limited to 1,4-diazines, as polyhalogenated pyridines and pyrimidines are recovered unchanged and pyridazines are hydrolyzed or oxidatively cleaved.[21] Although the yields are generally lower, 30% H_2O_2 can replace $K_2S_2O_8$ as the precursor to the actual oxidizing agent (Caro's acid). Therefore, the orientation of this oxidation is solely dependent on the strong acid medium.

The generally accepted mechanism of N-oxidation involves the nucleophilic attack of the lone pair of electrons on nitrogen on the outermost oxygen of the peracid (eq 2).[2-4] The progress



(2)

of the reaction depends primarily on the basicity (nucleophilicity) of the nitrogen atom and on the ability of the oxidizing agent to form a positively polarized (electrophilic) outermost oxygen. The orientation of the peracetic acid oxidation of chlorinated pyrazines (the exclusive formation of 2-chloro 4-oxide isomers) is governed by the relative basicities of the ring nitrogens.[2-5] In sulfuric acid at low pH, the equilibrium strongly favors the protonation of the most basic nitrogen, effectively eliminating it as a reaction center (eq 3).



(3)

Although the nucleophilicity of the remaining nitrogen is reduced by both the electron-withdrawing chlorine and protonated nitrogen, the electrophilicity of persulfuric acid is sufficient to effect oxidation. As with the peracetic acid case, the regiospecificity of the oxidation is controlled by the relative basicities of the pyrazine nitrogens.

Recent work has established that protonation of pyrazine and quinoxaline monooxides occurs preferentially on the unoxidized nitrogen atom.[22,23] This observation explains the inability to form bis *N*-oxides with any substrate except tetrachloropyrazine where perhalogen substitution sufficiently reduces the basicity of the unoxidized nitrogen to allow oxidation to compete with protonation.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were run on a T-60 spectrometer in $CDCl_3$ with a Me_4Si internal standard at a probe temperature of 39 °C. Elemental analyses were performed by Dow Analytical Services, Midland, Mich. The experimental data are summarized in Table II.[24,25] The following example is illustrative of the general synthetic procedure.

2,3-Dichloropyrazine 1-Oxide. To a stirred solution of 150 g (~1 mol) of 2,3-dichloropyrazine in 1 L of sulfuric acid at 10 °C is gradually added 300 g (~1.1 mol) of potassium persulfate. The reaction mixture is stirred for 24 h at room temperature and carefully poured into 3 L of ice water. The aqueous solution is extracted with chloroform and the extract is washed with bicarbonate solution and brine and then dried over magnesium sulfate. Evaporation of the solvent affords a white solid which is recrystallized from alcohol to give 140 g (85%) of white needles.

For lower halogenated pyrazines and quinoxalines, 30% hydrogen peroxide can be substituted for potassium persulfate with only small decreases in yield.

Note: Halogenated pyrazine N-oxides have been found to be severe skin and eye irritants and necessary precautions are required to prevent contact.

Supplementary Material Available. A table of the LIS shifts (1 page). Ordering information is given on any current masthead page.

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(24) Reported yields refer to recrystallized products following the prescribed workup. In general the aqueous solution of the reaction mixture is extracted with 1–2 volumes of chloroform. The organic layer contains the product and traces of unoxidized substrate. Because of the appreciable water solubility of the *N*-oxides, often significant quantities of product remain in the aqueous layer along with unknown water-soluble oxidation products. Continuous or repeated extraction significantly improves the isolated yields of all but the methyl derivatives.
(25) Satisfactory analytical data were reported for all new compounds listed in the table.
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Metal Ion Activation of Nitriles. Syntheses of 1,3-Bis(arylimino)isoindolines

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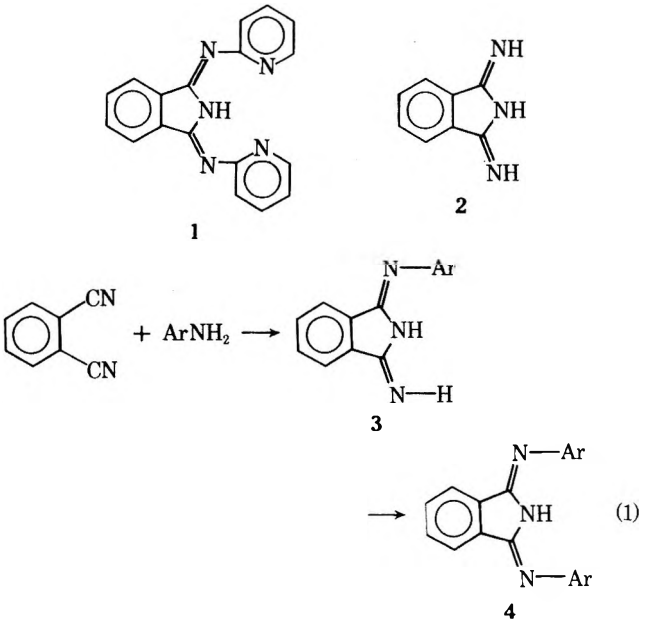
Two new syntheses utilizing metal ion facilitation for the preparation of 1,3-bis(arylimino)isoindolines (BAIIs) under mild conditions are described. Alkaline earth salts catalyze the nucleophilic addition of a large number of primary aromatic amines to phthalonitrile, to form both chelating and nonchelating BAIIs; the salts presumably function as Lewis acid type catalysts and may be applicable to a variety of nucleophilic additions to nitriles. Several divalent transition metal acetates and chlorides facilitate the addition to phthalonitrile of those primary aromatic amines which lead to formation of chelating BAIIs. In the latter case metal chelate complexes were isolated directly and experimental observations are consistent with the metal ion functioning, at least in part, as a template for the reactants. Treatment of the BAII metal chelate complexes with excess KCN liberates the free BAII ligand.

To avoid the formation of phthalocyanine and related pigment type by-products which frequently accompany the formation of 1,3-bis(arylimino)isoindolines (BAIIs) using previously reported syntheses, a method for catalyzing BAII formation under mild conditions was sought. Two new syntheses utilizing metal ion facilitation are reported here along with their application to the preparation of a series of new BAIIs.[1,2] One of the new methods of nitrile activation may be applicable to a variety of nucleophilic additions to the nitrile grouping.

The parent 1,3-bis(2-pyridylimino)isoindoline (1) was first prepared by Linstead et al. via the intermediate **2**, but was later prepared from phthalonitrile and 2-aminopyridine directly in a single step.[3,4] Variations of these methods have appeared but in general the initial nucleophilic addition of aromatic amine to phthalonitrile requires either severe reaction conditions, including high temperatures, or a catalyst.[5]

The addition of a primary amine to phthalonitrile results in an intramolecular cyclization to form a relatively stable 1-arylimino-3-iminoisoindoline **3**, which may undergo addition of a second amine with loss of ammonia and formation of the BAII **4** (eq 1).



When the amine is a 2-amino heterocycle, the monosubstituted diimine **3** is more reactive toward addition of a second amine, and accordingly is less easily isolated. An attempt to selectively prepare unsymmetrical BAIIs, by taking advantage of the stepwise nature of their formation, was unsuccessful.

Results and Discussion

Alkaline Earth Salt Catalysis. Several alkaline earth salts were found to facilitate the addition of primary aromatic amines to phthalonitrile under mild conditions. The *homogeneous* system obtained with $CaCl_2$, $Mg(ClO_4)_2$, or MgI_2 in alcoholic solvents was effective for the synthesis of a variety of BAIIs as indicated in Tables I and II, and in catalyzing some related amine–nitrile addition reactions. In general, product yields were dependent on the solvent, alkaline earth salt, and to a lesser extent on the amine.

Effect of Solvent. Alcohols appear to be the preferred solvents; satisfactory product yields and reaction times were observed with 10 mol % of catalyst in refluxing 1-butanol (Table II). Catalysis by calcium chloride was also observed in lower boiling alcohols but reaction rates were too slow for synthetic utility. In other polar solvents such as methyl ethyl ketone, acetonitrile, or dimethylformamide, the phthalonitrile could be recovered unreacted, although a reaction was observed in some aromatic solvents.

Magnesium perchlorate also facilitates the synthesis of BAIIs in aromatic solvents (benzene, toluene) but the activation of phthalonitrile under such *heterogeneous* conditions required stoichiometric quantities as indicated in Table III. Adding a small amount (10%) of ethanol to the benzene did not raise the yield; suggesting that the alcohol does not play an important part in the activation by alkaline earth salts. The reaction in aromatic solvents frequently afforded a small amount of insoluble orange crystals which analyzed for MgL_2 (where L = the conjugate base of 1). The infrared spectrum (KBr) of the orange crystals was similar to that observed for free BAII 1 but with a reduction in intensity of the 1630 cm^{-1} band and the appearance of a new band at 1530 cm^{-1}; similar changes in spectra are observed on coordination of 1 to transition metal ions. Treatment of the orange crystals with ammonium chloride gave free BAII 1 and alternatively treatment with cupric acetate afforded the corresponding metal complex, CuLOAc. The limited solubility of the orange crystals precluded further characterization by solution spectroscopic methods but the data suggest that the crystals are probably a magnesium(II) adduct of BAII 1.

Effect of Alkaline Earth Salt. Magnesium iodide was an active catalyst, although its deliquescent nature made it unsuited for general use. Anhydrous magnesium perchlorate (Anhydrone) has a superior shelf life and a higher catalytic activity but the explosion hazard associated with its use reduces its synthetic utility.[6] Calcium chloride (both dihydrated and anhydrous) was an active catalyst in alcoholic solvents and of the several active alkaline earth salts anhydrous calcium chloride was the catalyst of choice as shown in Table II.

Effect of Amine. Calcium chloride catalysis was applied

Table I. Yield Data, $CaCl_2$-Catalyzed Syntheses of 1,3-Bis(arylimino)isoindolines

Compd no.	Registry no.	Amine[a]	Registry no.	Yield,[b] %	Color	Mp, °C	Anal.[c]
1	14526-01-3	2-Aminopyridine	504-29-0	76	Yellow	181–183	
8	61702-00-9	2-Amino-3-methylpyridine	1603-40-3	82	Yellow	135–136	C, H, N
9	61702-01-0	2-Amino-4-methylpyridine	695-34-1	84	Yellow	165–166	C, H, N
10	61702-02-1	2-Amino-5-methylpyridine	1603-41-4	85	Yellow	215–216	C, H, N
11	61702-03-2	2-Amino-6-methylpryridine	1824-81-3	95	Yellow	136–137	C, H, N
12	61702-04-3	2-Amino-4,6-dimethylpyridine	5407-87-4	78	Yellow	137–138	C, H, N
13	61702-05-4	2-Amino-4-ethylpyridine	33252-32-3	66	Yellow	105–106	C, H, N
14	61702-06-5	2-Amino-4-propylpyridine	61702-15-6	47	Yellow	70–71	C, H, N
15	61702-07-6	2-Amino-4-*sec*-butylpyridine	61702-16-7	72	Yellow	105–106	C, H, N
16	61702-08-7	2-Amino-4-*tert*-butylpyridine	33252-26-5	48	Yellow	234–235	C, H, N
17	61702-09-8	2-Amino-4-amylpyridine	60781-86-4	71	Yellow	101–102	C, H, N
18	61702-10-1	2-Amino-5-chloropyridine	1072-98-6	46	Yellow	243–244.5	C, H, N
19	61702-11-2	2-Amino-5-bromopyridine	1072-97-5	27	Yellow	246–247.5	C, H, N
20	61702-12-3	2-Amino-5-nitropyridine	4214-76-0	67	Gold	308–310	C, H, N
21	16612-53-6	2-Aminothiazole	96-50-4	25	Gold	260–261	C, H, N
22	61702-13-4	2-Amino-4-methylthiazole	1603-91-4	36	Gold	241–244	C, H, N
23	61702-14-5	3-Aminopyridine	462-08-8	67	Yellow	182–183	
24	32313-77-2	Aniline	62-53-3	20	Yellow	128–129	

[a] See Experimental Section for general reaction conditions; amines were commercially available or their preparation is given in the Experimental Section. [b] Yield of recrystallized product. [c] New compounds analyzed for the elements indicated to within ±0.3% of calculated values.

Table II. Effect of Alkaline Earth Salt on Yield of BAII

Amine	Catalyst	Catalyst/ phthalonitrile	Solvent	Yield, %
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	EtOH	6.5
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	PrOH	26
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	BuOH	60
2-Aminopyridine[b]			BuOH	2
2-Aminopyridine[b]	$CaCl_2 \cdot 2H_2O$	0.1	BuOH	48
2-Aminopyridine[b]	MgI_2	0.1	BuOH	34
2-Aminopyridine[b]	$Mg(ClO_4)_2$	0.1	BuOH	58
2-Aminopyridine[b]	$CaCl_2$	0.1	BuOH	76

[a] Experimental conditions: 2 mmol of phthalonitrile, 5 mmol of amine, and stated amount of catalyst were heated in 20 mL of solvent at reflux for 48 h. [b] Experimental conditions: 5 mmol of phthalonitrile, 10.5 mmol of amine, and stated amount of catalyst were heated in 10 mL of solvent at reflux for 48 h.

Table III. Alkaline Earth Salt Catalysis in Hydrocarbon Solvents[a]

Amine	Catalyst	Catalyst/ nitrile	Solvent	Reflux time, h	Yield, %
2-Aminopyridine	$Mg(ClO_4)_2$	0.1	C_6H_6[b]	48	9[c]
2-Amino-4-methylpyridine	$Mg(ClO_4)_2$	0.1	C_6H_6	48	10[c]
2-Aminopyridine	$Mg(ClO_4)_2$	0.1	(1:10) EtOH–C_6H_6	24	2.5
2-Aminopyridine	$Mg(ClO_4)_2$	0.5	C_6H_6	48	37[c]
2-Aminopyridine	$Mg(ClO_4)_2$	1.0	C_6H_6	48	50
2-Aminopyridine	$CaCl_2$	0.5	C_6H_6	48	<1

[a] Experimental conditions: 10 mmol of phthalonitrile, 21 mmol of amine, and stated amount of catalyst were refluxed in 20 mL of solvent. [b] Similar yield was obtained in toluene. [c] Average of two or more runs.

to the addition of a variety of primary aromatic amines to phthalonitrile resulting in the synthesis of a number of new chelating and nonchelating BAIIs as shown in Table I. The reactivity of amines toward calcium chloride catalysis paralleled that observed toward alkoxide catalysis with the exception of aniline, which was less reactive with calcium chloride. 2-Aminopyrimidine and 2-amino-6-methylpyrimidine were unreactive toward both alkoxide and calcium chloride catalysis, an observation ascribed to the presumably low nucleophilicity of the amino groups. The yield data in Table I suggest that 2-aminopyridines bearing electron-withdrawing substituents and amino heterocycles where the cycle contains more than one heteroatom are less reactive substrates than 2-aminopyridine itself and alkylated 2-aminopyridines. Thus the data suggest that the prime requisite of the amine is associated with its nucleophilicity.

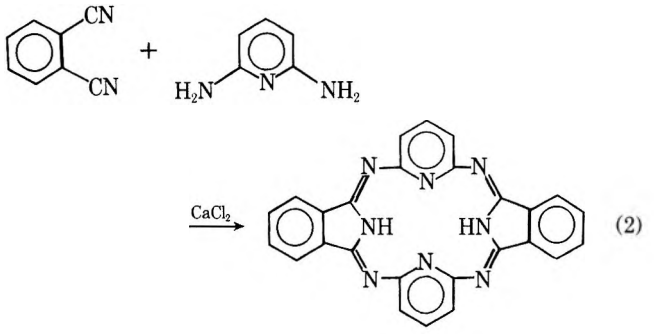
Mechanism. While the details of the mechanism of activation remain uncertain, it seems that at least in alcoholic solvents the alkaline earth salts function as Lewis acid type catalysts. Organonitrile complexes with a variety of metal ions including some of the alkaline earth cations (e.g., Be and Mg) are known.[7–9] The most common form of bonding between nitriles and metal ions is thought to be linear with the metal center coordinated to the nitrogen lone pair,[7] resulting in

polarization of the carbon–nitrogen bond; with some transition metal ions this leads to significant activation of the bond toward nucleophilic addition.[10] Spectroscopic studies have shown that alkaline earth cations perturb the C≡N stretching frequency in the same manner that Lewis acids do;[11] thus it seems likely that alkaline earth cations functioning as weak Lewis acids could activate the nitrile C≡N bond. Lewis acid catalysts have been employed to catalyze a number of amine to nitrile addition reactions in recent years.[12–14]

Earlier, Meyers et al. reported the use of *stoichiometric* amounts of magnesium perchlorate (in aromatic solvents) to facilitate the intramolecular cyclization of enamine nitriles.[6,15,16] The magnesium perchlorate facilitated addition of primary amines to phthalonitrile in aromatic solvents described above may be related to the observation by Meyers, but the reaction in alcoholic solvents is seemingly homogeneous and catalytic suggesting a different role for the metal cation.

There is no evidence to suggest that the alkaline earth cation facilitates addition of the second amine. The intermediate **3** was observed spectroscopically in solution and could be isolated; its conversion to the BAII **1** under the usual reaction conditions did *not* require the presence of a catalyst.

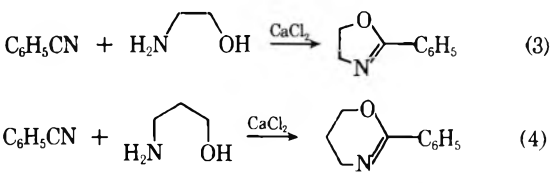
Application. The generality of alkaline earth salt activation of nitriles toward amine addition was evident from the effect of calcium chloride on some other nitrile–amine reactions. Calcium chloride successfully catalyzed the addition of 2,6-diaminopyridine to phthalonitrile to form macrocycle **5** in 70% yield (eq 2).[17]



(2)

5

Calcium chloride also catalyzed the synthesis of 2-substituted 2-oxazolines and 4*H*-5,6-dihydrooxazines (eq 3 and 4). Treating benzonitrile and 2-aminoethanol with 10 mol % $CaCl_2$ at 110–120 °C afforded 2-phenyl-2-oxazoline in 92% yield (isolated). Similar treatment of 3-aminopropanol and benzonitrile with $CaCl_2$ gave a 67% yield of 2-phenyl-4*H*-5,6-dihydrooxazine. (These synthetic intermediates had previously been isolated in 85 and 72% yields, respectively, after nitrile activation by the Lewis acids $Cd(OAc)_2 \cdot 2H_2O$ and $ZnCl_2$[12].) Thus it appears that alkaline earth cations may be useful as mild catalysts toward a number of nucleophilic additions to organonitriles.



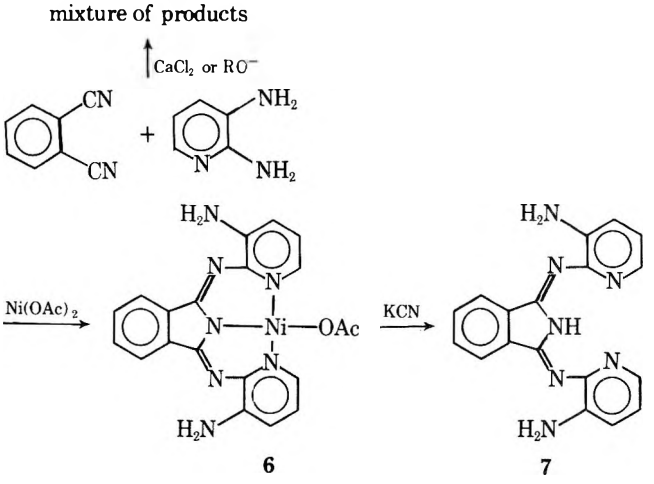
(3)

(4)

Transition Metal Ion Facilitated Synthesis of BAIIs. Several divalent first row transition metal salts facilitate the addition of primary aromatic amines to phthalonitrile to form *chelating* BAIIs which are isolated as the corresponding metal chelate complexes, ML(X).[1b] The experimental conditions are mild and yields may be quite favorable. Treatment of the BAII–metal complex with excess KCN liberates the free BAII ligand, thus affording a two-step sequence for the synthesis of chelating BAIIs.

An Example. The synthetic utility of this approach is best illustrated by the preparation of the BAII chelating ligand obtained from 2,3-diaminopyridine via the template formation of NiL′(OAc) (Scheme I). The products expected from

Scheme I



phthalonitrile and 2,3-diaminopyridine when using a catalyst which does not discriminate between the two amino groups include three BAIIs and the 2:2 macrocycle analogous to **5**. Using the template approach, adduct formation between phthalonitrile and 2,3-diaminopyridine was directed stereochemically to favor the chelated BAII **6**. The template product **6** was subsequently treated with potassium cyanide to afford **7**, the only BAII product isolated.

Effect of Solvent. Refluxing phthalonitrile with 2.1 equiv of amine and 1 equiv of transition metal salt in methanol or ethanol (the mildest conditions of any of the BAII preparations) afforded the BAII metal chelate complexes, ML(X), in yields as high as 75%. With the exception of the special cases discussed below, the use of higher boiling alcohols did not improve the yield. The use of other low-boiling organic solvents was limited by the poor solubility of transition metal salts but the reaction was successfully run in the donor solvent pyridine. Increasing the ratio of phthalonitrile or amine to metal ion did significantly increase the yield. The only side products isolated were small amounts of metallophthalocyanines.

Effect of Metal Ions and Counterions. The direct synthesis of BAII metal chelate complexes was observed with divalent Co, Ni, Cu, and Zn salts. The yields of metal complex obtained with Co, Ni, and Cu ions were significantly higher than with Zn (Table IV), an observation which may be associated with the strong preference of Zn(II) for tetrahedral coordination geometry. For 2-aminopyridine and most ring-alkylated 2-aminopyridines the yields of ML(OAc) were comparable for Co, Ni, and Cu, but with certain aromatic amines (e.g., 2-aminothiazole, 2,3-diaminopyridine, and 2-amino-6-methylpyridine) yields were more sensitive to the selection of the metal ion; in such cases $Ni(OAc)_2$ was usually the metal salt of choice. No determined effort was made to expand the list of metal ion facilitators although stable BAII complexes have also been formed with second and third row transition metal ions.[2,18]

Only metal salts with the counterions OAc^- and Cl^- were studied. The acetate complexes, ML(OAc), were very stable. With chloride as the counterion a mixture of complexes was obtained, probably ML(Cl), ML(OH), and ML(OR) resulting from partial anion exchange with the solvent alcohol. Treat-

Table IV. Representative Yield Data for Metal-Template Syntheses of BAII Complexes[a]

Amine	Metal salt	Product	Solvent	Reflux time, h	Yield,[b] %
2-Aminopyridine			EtOH	1200	0
2-Aminopyridine	$Co(OAc)_2 \cdot 4H_2O$	CoL(OAc)	EtOH	48	55
2-Aminopyridine	$Zn(OAc)_2 \cdot 2H_2O$	ZnL(OAc)	EtOH	72	7
2-Aminopyridine	$NiCl_2 \cdot 6H_2O$	"NiL(Cl)"	EtOH	48	50
2-Aminopyridine	$Ni(OAc)_2 \cdot 4H_2O$	NiL(OAc)	Pyridine	24	23
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$	CuL'(OAc)	EtOH	6	50
2-Amino-6-methylpyridine	$Ni(OAc)_2 \cdot 2H_2O$		EtOH	24	0
2-Amino-6-methylpyridine	$Ni(OAc)_2 \cdot 4H_2O$ (+$CaCl_2$)	NiL'(OAc)	EtOH	24	33
2-Amino-6-methylpyridine	$NiCl_2 \cdot 6H_2O$	"NiL'Cl"	PrOH	72	64
2-Aminothiazole	$Ni(OAc)_2 \cdot 4H_2O$	NiL'(OAc)	MeOH	24	42
2-Amino-4-methylthiazole	$Ni(OAc)_2 \cdot 4H_2O$		EtOH	24	0
3-Aminopyridine	$NiCl_2 \cdot 6H_2O$		EtOH	24	0

[a] Conditions: 2 mmol of phthalonitrile, 2 mmol of metal salt, 4.2 mmol of amine, and 10 mL of solvent. [b] For crude reaction product suitable for treatment with KCN.

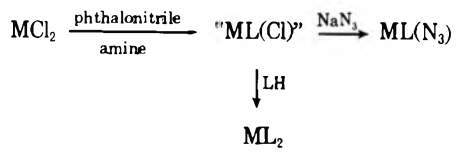
Table V. Yield Data for Two-Step Template–KCN Synthesis of Chelating BAIIs

Amine	Metal salt	Yield data, %		
		Template step[a]	KCN rxn[a]	Overall[b]
2-Aminopyridine	$Ni(OAc)_2 \cdot 4H_2O$		96	
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$		99	
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$	(69)[c]		48
2-Amino-6-methylpyridine	$NiCl_2 \cdot 6H_2O$	(60)[c]		44
2-Amino-5-bromopyridine	$Cu(OAc)_2 \cdot 2H_2O$	(55)[c]		27
2-Aminothiazole	$Cu(OAc)_2 \cdot 2H_2O$			42
2,3-Diaminopyridine	$Ni(OAc)_2 \cdot 4H_2O$			15

[a] For experimental conditions see the Experimental Section. [b] Based on phthalonitrile. [c] Yield of crude product.

ment of the mixture with a strongly nucleophilic anion (e.g., N_3^-) resulted in conversion to a homogeneous material, $ML(N_3)$. Similarly, treatment of the mixture "NiL(Cl)" with added BAII ligand afforded the known material,[3,18] ML_2, with ligand:metal ion stoichiometry of 2:1 (Scheme II).

Scheme II



Effect of Amine. The choice of aromatic amine appeared to be limited to amines which form tridentate chelating BAIIs. Amines which failed under the usual conditions for transition metal facilitated BAII synthesis were (a) those which lacked an annular nitrogen with an amino group in the α position (e.g., aniline, 3-aminopyridine); (b) those which satisfied (a) but lacked an amino group of sufficient nucleophilicity (e.g., 2-aminopyrazine, 2-aminopyrimidine); and (c) those which satisfied both (a) and (b) but contained a relatively bulky substituent in the other position α to the ring heteroatom (e.g., 2-amino-6-methylpyridine, 2-amino-4-methylthiazole). The limitation (c) was in some cases overcome by the use of increased reaction temperatures as shown in Table IV.

Treatment of the BAII Complex with Potassium Cyanide. Treatment of the template product, ML(X), with excess potassium cyanide in an appropriate solvent afforded the free BAII ligand in almost quantitative yield. No external source of proton was required; apparently the BAII anion is readily protonated by solvent or traces of moisture present. Ethanol was the solvent of choice with the more soluble complexes and dimethylformamide with the less soluble.

Yield data are reported in three columns of Table V. In the first, the values refer to crude BAII–metal complex as isolated from the template reaction. Values in the second column refer only to yields from treatment of purified BAII metal chelate complex with KCN, and values in the last column refer to the overall two-step sequence of BAII preparation without purification of the intermediate BAII metal chelate complex.

The BAII ligands obtained via the two-step sequence were identical with those prepared by other methods; in general, yields were lower than for the $CaCl_2$-catalyzed reaction except for special cases where the transition metal ion directed the course of the reaction to selectively favor one available amino group over another as illustrated in Scheme I.

The Role of the Metal Ion. Our conclusions are based primarily on the observation that, unlike the $CaCl_2$-catalyzed reaction, the transition metal catalyzed reaction imposed stereochemical restrictions on the amine.

It appears that the aromatic amine must be a nitrogen heterocycle with a relatively nucleophilic amino group α to the annular N atom but with no bulky substituent in the other position α to the annular nitrogen.

These stereochemical requirements coupled with the very mild reaction conditions contrast with the requirements for the $CaCl_2$-catalyzed reaction and suggest that a different type of metal ion activation is in operation.

Although it is difficult to unambiguously document the role of the transition metal ion as a template, the following sequence is both plausible and consistent with experimental data. Almost certainly the initial step on mixing involves formation of a metal 2-aminopyridine complex in which the pyridine is coordinated via the ring nitrogen.[19] If the free amino group is in the α position it is in a position stereochemically favored for interaction with a nitrile group coordinated in an adjacent coordination site; a free amino group

in the β or γ positions could not take advantage of this type of intramolecular interaction. (The activation of nitriles toward nucleophilic attack by coordination to transition metal ions is well known.[10]) A bulky substituent in the other α position of the heterocycle is likely to result in changes in the stereochemistry of the coordination sphere. In general, steric interactions associated with coordination of 2,6-disubstituted pyridines are relieved by a reduction in the number of ligands about the metal center or by coordination of the pyridine such that the plane of the ring is perpendicular to the plane of the metal and other donor atoms.[20,21] This modification of the coordination sphere could make interaction of the α-amino group with a coordinated nitrile less favorable. The different roles of the transition metal and alkaline earth ions appear to be related to the presence or absence of a metal ion–amine interaction during the formation of the BAII.

An ancillary experiment was run in which a catalytic amount (10 mol %) of anhydrous calcium chloride was added to the standard template reaction on a hindered amine (2-amino-6-methylpyridine); this resulted in the isolation of the BAII metal complex, NiL'(OAc), in 35% yield. In the absence of calcium chloride no complex formation was observed, presumably because the hindered aminopyridine could not achieve the favored coordination geometry for the template effect to occur. With calcium chloride present, the calcium chloride functioned as a Lewis acid type catalyst and activated the nitrile toward attack by the free amino group. The BAII chelating ligand was formed free in solution and was subsequently scavenged by the nickel acetate to form NiL'(OAc). This result further illustrates the difference in mechanism of action between alkaline earth ions and transition metal ions in the formation of BAIIs.

Conclusions

Two new methods employing metal ion facilitation have been reported for the synthesis of 1,3-bis(arylimino)isoindoline, BAII, chelating ligands. The first method involves facilitation by alkaline earth salts in alcoholic solvents and may operate by Lewis acid type activation of the C≡N bond. This method of activation was extended to the preparation of the 2-oxazoline and the 4*H*-5,6-dihydrooxazine derived from benzonitrile and the appropriate amino alcohol, indicating that the application of alkaline earth salt catalysis to nucleophilic addition of amines to nitriles may be of general utility. In the second method transition metal salts stoichiometrically facilitate the synthesis of chelating BAIIs which are isolated as the corresponding metal complexes. The transition metal ions facilitate the addition of certain aromatic 2-amino heterocycles to phthalonitrile under mild conditions seemingly by a transition metal template effect. The BAII ligand may be freed from the complex by treatment with potassium cyanide.

The chemical and physical characterization of BAII–transition metal chelate complexes will be discussed in a forthcoming publication.

Experimental Section

Phthalonitrile and the aromatic amines were obtained from commercial sources (and were used as obtained) unless noted otherwise. Infrared spectra were recorded for KBr pellets on a Perkin-Elmer Model 457 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard and were reported in parts per million downfield from Me_4Si; the spectrometer was a JEOL Model JNM-100. Visible spectra were recorded on a Cary Model 15 spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory.

Purification and Characterization of BAIIs. The BAIIs are yellow or gold, crystalline materials of seemingly indefinite shelf life. Although sensitive to acid they are stable at least to mild base and have considerable thermal stability especially when coordinated to transition metal ions. They are insoluble in water and soluble in organic solvents; the solubilities of BAIIs in organic solvents usually increase with the presence of alkyl substituents and decrease with the presence of electronegative substituents or two heteroatoms in the aryl groups.

Unreacted starting materials may usually be removed by washing of the dry reaction product with water followed by recrystallization of the residue from ethanol-water. The most persistent impurity is phthalocyanine, formed by self-condensation of phthalonitrile, which when solubility permits is conveniently removed by dissolving the impure BAII in chloroform and filtering through a fine glass frit or a short column of alumina.

In general the intensely colored BAIIs have an ϵ of 19 000–22 000 for λ_{max} in the visible region.[3] The infrared spectra of the aminopyridine derived BAIIs usually contain a very strong $\nu_{C=N}$ in the 1650–1600 cm^{-1} region and four moderate-strong bands in the 1600–1400 cm^{-1} region ascribed to pyridyl skeletal vibrations.[22] NMR spectra were recorded where solubility permitted and representative data are shown in Table VI. The NMR spectra support the BAII structure; in many cases signals for the aryl hydrogens are well separated and assignments can be made. On the benzene ring the α hydrogens appear at lower field than the β hydrogens, presumably owing to deshielding by the imino C=N π-electron cloud.[23] For BAII derived from ring-alkylated aminopyridines the pyridyl hydrogens are usually shifted downfield from Me_4Si in the following order: $H_5 < H_3 < H_4 < H_6$. Carbon, hydrogen, and nitrogen analyses consistent with the indicated stoichiometry were obtained for all new BAII as indicated in Table I.

2-Amino-4-alkylpyridine. These amines were prepared by the method of Case and Kasper[24] from 4-alkylpyridine and sodium amide (Fisher Scientific Co.): 4-ethyl, 55% yield, mp 66–70 °C (lit. 70–71 °C[24]); 4-propyl, 50% yield, as deliquescent white crystals stored in a desiccator over Drierite;[25] 4-*tert*-butyl, 12%, mp 82–83 °C; 4-amyl, 58% yield, colorless crystals, mp 55–56 °C (lit.[26] 58–58.5 °C).

4-*sec*-Butylpyridine. A method similar to that of Brown and Murphey was employed.[27] Approximately 500 mL of NH_3 was condensed in a 1-L flask; 1 mol of sodium amide (Fisher) followed by 1.0 mol of 4-ethylpyridine was added to the flask. After stirring under NH_3 reflux for 30 min, 1.1 mol of ethyl iodide was added via an addition funnel to the orange-red suspension over a 1.5-h period. Stirring was continued after the ethyl iodide addition was complete and the solvent was allowed to evaporate slowly. Water (50 mL) was added to the residue and the layers were separated. The aqueous layer was extracted with ether and the combined organic layers were dried over Na_2CO_3, concentrated, and distilled. A colorless oil, 117.2 g (87%), bp 120–125 °C (90 mm) [lit.[27] 128–130 °C (100 mm)], was collected. The oil exhibited an NMR signal typical for a *sec*-butyl group in addition to the usual pattern for 4-substituted pyridine.

2-Amino-4-*sec*-butylpyridine. This new 2-aminopyridine was prepared according to the general procedure of Case and Kasper[24] from 4-*sec*-butylpyridine (described above). The product was obtained as white crystals (49%): mp 64–65 °C; NMR ($CDCl_3$) δ 7.9 (d) 1 H, 6.44 (d) 1 H, 6.29 (s) 1 H, 4.66 (s, br) 2 H, 2.48 (m) 1 H, 1.54 (m) 2 H, 1.19 (d) 3 H, 0.94 (t) 3 H.

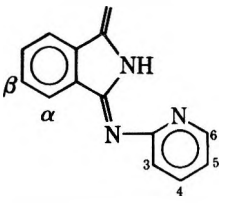
Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.97; H, 9.32; N, 18.70.

1-(2-Pyridylimino)-3-iminoisoindoline (3). Phthalonitrile (10 mmol), 10 mmol of 2-aminopyridine, and 60 mg of sodium methoxide in 100 mL of ethanol were heated at reflux for 48 h. The visible spectrum showed a ratio of λ_{max} 3360/λ_{max} 4060 at 3.6. Upon cooling the solution was concentrated in vacuo. The residue was taken up in EtOAc–CH_2Cl_2 and chromatographed over alumina. Elution with CH_2Cl_2 and with EtOAc removed unreacted phthalonitrile and the BAII but left **3** on the column. Elution with 3/1 CH_2Cl_2–EtOH eluted **3**. Concentration of the eluent afforded 617 mg (28% yield) of yellow powder, mp 138–140 °C, λ_{max} (EtOH) 3360 (ϵ 13 200).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.04; H, 4.74; N, 25.25.

Reaction of 1-(2-Pyridylimino)-3-iminoisoindoline (3) with 2-Amino-4-methylpyridine. A 115-mg (0.505 mmol) sample of **3** and 1.0 mmol of 2-amino-4-methylpyridine were heated in refluxing *n*-BuOH for 12 h. TLC analysis (SiO_2, EtOAc) indicated only a single yellow spot (R_f 0.5–0.6). The solvent was allowed to evaporate at room temperature and the residue was washed with water, dried, and then dissolved in hot EtOH. On cooling 66 mg of fine yellow needles deposited, mp 169–170 °C. Recrystallization of the needles from benzene–hexane left the melting point unchanged. NMR analysis ($CDCl_3$) showed a ratio of alkyl (singlet) hydrogen to aromatic hydrogen of 1/18 in contrast to the 3/11 ratio expected for the simple addition product.

Table VI. Selected Chemical Shift Data for New Chelating BAII Ligands



Compd no.	Derived from (amine)	Solvent	Chemical shifts[a] H_α	H_β	H_3	H_4	H_5	H_6	Substituent
8	2-Amino-3-methylpyridine	$CDCl_3$	8.14 (m)	7.68 (m)[b]		7.67 (m)[b]	7.05 (q)	8.48 (d) $J = 5$	2.65 (s)
9	2-Amino-4-methylpyridine	$CDCl_3$	7.98 (m)	7.50 (m)	7.22 (s)		6.84 (d)	8.36 (d) $J = 4$	2.37 (s)
10	2-Amino-5-methylpyridine	$CDCl_3$	8.00 (m)	7.55 (m)[b]	7.31 (d)	7.56 (m)[b]		8.37 (s)	2.40 (s)
11	2-Amino-6-methylpyridine	$CDCl_3$	8.16 (m)	7.71 (m)	7.28 (d) $J = 7.5$	7.7 (m)	7.02 (d) $J = 8.0$		2.61 (s)
12	2-Amino-4,6-dimethylpyridine	$CDCl_3$	8.12 (m)	7.68 (m)	7.09 (s)		6.84 (s)		2.40 (s), 2.56 (s)
13	2-Amino-4-ethylpyridine	$CDCl_3$	8.18 (m)	7.70 (m)	7.43 (s)		7.05 (d)	8.57 (d) $J = 5$	α 2.78 (q) β 1.34 (t)
14	2-Amino-4-propylpyridine	$CDCl_3$	7.98 (m)	7.50 (m)	7.20 (s)		6.82 (d)	8.38 (d) $J = 5$	α 2.61
7[c]	2,3-Diaminopyridine[d]	C_5D_5N	8.25 (m)[b]	7.64 (m)		7 39 (d)	7.12 (q)	8.25[b]	H_2N 6.13 (s)
22	2-Amino-4-methylthiazole	$CDCl_3$	7.73 (q)	7.54 (q)	6.70 (s)				2.58 (s)

[a] Chemical shifts are reported in parts per million downfield from Me_4Si, the internal standard. [b] Overlapping signal. [c] Registry no., 61702-17-8. [d] Registry no., 452-58-4.

2-Phenyl-2-oxazoline. In a round-bottom flask, 0.1 mol of benzonitrile, 0.2 mol of 2-aminoethanol, and 0.01 mol of anhydrous calcium chloride were heated with stirring under argon for 8 h at 110–120 °C (much longer reaction times resulted in reduced yield with the formation of nonvolatile products). The reaction mixture was distilled under reduced pressure to afford a fraction of colorless oil [bp 75–84 °C (2–3 mm)] which analyzed for a single component by VPC. The IR and NMR spectra of the oil were consistent with the structure of 2-phenyl-2-oxazoline; the yield was 13.6 g (92%).

2-Phenyl-4*H*-5,6-dihydrooxazine. In a round-bottom flask, 0.1 mol of benzonitrile, 0.15 mol of 3-aminopropanol, and 0.01 mol of anhydrous calcium chloride were heated with stirring at 110–120 °C for 20 h. The viscous, yellow reaction product was distilled under reduced pressure and a fraction was collected of colorless oil [bp 95–115 °C (ca. 2 mm)], 10.8 g (67% yield), which analyzed for a single component by VPC and exhibited IR and NMR spectra consistent with the structure of 2-phenyl-4*H*-5,6-dihydrooxazine.

General Preparation for BAIIs Using Alkaline Earth Salts. In a round-bottom flask outfitted with a reflux condensor, 10 mmol of phthalonitrile. 21 mmol of primary aromatic amine, and 1 mmol of alkaline earth salt along with 20 mL of 1-butanol were heated at reflux for 48 h. On cooling the BAII product frequently crystallized from solution. The BAII was usually recrystallized from ethanol or ethanol–water; other recrystallization solvents employed include chloroform–hexane and pyridine–ethanol. If the BAII did not crystallize from 1-butanol the solvent was allowed to evaporate, and the residue was washed with water, dried, and recrystallized from ethanol–water.

Small amounts of phthalocyanine, which occasionally accompanied BAII formation, were removed by taking up the impure BAII in chloroform and filtering through a fine glass frit or through a short column of alumina.

Analysis for Low Yields of BAII. When the preparation afforded only a low yield of BAII, the yield was most easily quantified spectroscopically. The 1-butanol was allowed to evaporate and the residue was washed with water, dried, and then dissolved in ethanol. After appropriate dilution the absorption at 384 nm was recorded and the concentration was determined using ϵ 21 800 as determined for pure 1.

Isolation of a Mg–BAII Complex. Five millimoles of phthalonitrile, 10.5 mmol of 2-aminopyridine, and 5 mmol of magnesium perchlorate (Anhydrone) in 10 mL of benzene were heated at reflux for 48 h. After cooling the solvent was allowed to evaporate at room temperature and the residue was washed with water. After drying, the residue (1105 mg of yellow powder) was extracted with hot ethanol leaving behind 535 mg of orange, crystalline powder. The infrared spectrum of the orange powder was similar to that of NiL(OAc). The powder analyzed for MgL_2. Anal. Calcd for $C_{16}H_{24}N_{10}Mg$: C, 69.63; H, 3.90; N, 22.56. Found: C, 69.40; H, 4.18; N, 22.28.

The ethanol extract described above was analyzed spectrophotometrically and contained 0.87 mmol of BAII 1.

A small amount of orange powder was treated with excess ammonium chloride in ethanol–water (10/1) and heated for 2 h. The orange crystals gradually went into solution and on cooling yellow needles deposited, identified as BAII 1, mp 182–183 °C.

General Preparation for BAII Chelate Complexes Using Transition Metal Salts. In a round-bottom flask outfitted with a reflux condensor, 2 mmol of phthalonitrile, 4.2 mmol of primary aromatic amine, and 2 mmol of transition metal dichloride or diacetate along with 10 mL of ethanol (or methanol) were heated at reflux generally for not more than 24 h. After the reaction mixture was allowed to cool, it was filtered and the residue was washed with water, alcohol, and acetone or ether. After drying, the residue (which was often crystalline) was suitable for direct use in the KCN reaction. This residue was essentially identical spectroscopically (IR, visible) with material prepared from treatment of the metal salt with the appropriate chelating BAII. The purification and chemical characterization of transition metal–BAII complexes will be discussed in a forthcoming publication.

Treatment of BAII–Metal Complexes with KCN. A. In a beaker 0.9 mmol of recrystallized (toluene) CuL′(OAc) derived from BAII **9**, 4 mmol of potassium cyanide, and 10 mL of ethanol were stirred at room temperature. After 5 h an additional 2 mmol of KCN was added. The disappearance of CuL′(OAc) (R_f 0.1) and the appearance of free L′H (**9**) (R_f ca. 0.5) was followed by TLC (silica gel, ethyl acetate). After 9 h the solvent was allowed to evaporate at room temperature and the residue was thoroughly washed with water. The residue consisted of a quantitative yield of fine, yellow needles, mp 164–165 °C (for authentic **9**, mp 165–166 °C).

B. The tan-brown powder (753 mg) obtained from a 2 mmol scale template preparation of NiL′(OAc), where L′ is derived from BAII **21**, 20 mmol of potassium cyanide, and 10 mL of dimethylformamide were heated at reflux for 36 h. Upon cooling 40 mL of water was added; the mixture was filtered, washed with water, and dried. The residue was treated with hot chloroform and filtered through a fine glass frit to remove a small amount of phthalocyanine type material. From chloroform–ethanol yellow-gold needles of BAII **21** were obtained in an overall yield of 60% for the two-step sequence.

Preparation of BAII 7 Derived from 2,3-Diaminopyridine. In a round-bottom flask outfitted with a reflux condensor 6 mmol of phthalonitrile, 12.3 mmol of 2,3-diaminopyridine, 6 mmol of $Ni(OAc)_2 \cdot 4H_2O$, and 30 mL of methanol was stirred at room tem-

perature for 2 h and then heated at reflux for 48 h. After cooling to room temperature the mixture was filtered and washed with water to afford after drying 1790 mg of brown, crystalline powder.

A 400-mg sample of the brown powder and 650 mg of KCN in 10 mL of chloroform and 7 mL of methanol was stirred at room temperature for 48 h. TLC (silica gel, ethyl acetate) indicated at least three components. After the solvent was allowed to evaporate, the residue was washed thoroughly with water and dried to afford 306 mg of brown powder. The brown residue was extracted with hot benzene and the extract was chromatographed over silica gel. Elution with 10/1 benzene–CH_2Cl_2 and with 10/1 benzene–EtOAc eluted an orange band which upon concentration gave orange crystals of BAII 7, mp 221.5–224 °C. The yield was 15% based on phthalonitrile. The infrared spectrum was consistent with the usual pattern for BAII and NMR data are included in Table VI. No other BAII products were observed, suggesting that either they were not formed or that if formed they had very unexpected solubility and chromatographic properties.

When phthalonitrile and 2,3-diaminopyridine were treated with $CaCl_2$ according to the procedure given earlier, a mixture of products was obtained. TLC analysis (SiO_2, ethyl acetate) of the mixture did not indicate the presence of 7; however, we are unable to say with certainty if any other BAII products were present.

Acknowledgment. Unmitigated encouragement from and very helpful discussions with Dr. Lee Robert Mahoney are gratefully acknowledged.

Registry No.—**3**, 61702-18-9; phthalonitrile, 91-15-6; Mg BAII complex, 61846-66-0.

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Substituent Rearrangement and Elimination during Noncatalyzed Fischer Indole Synthesis

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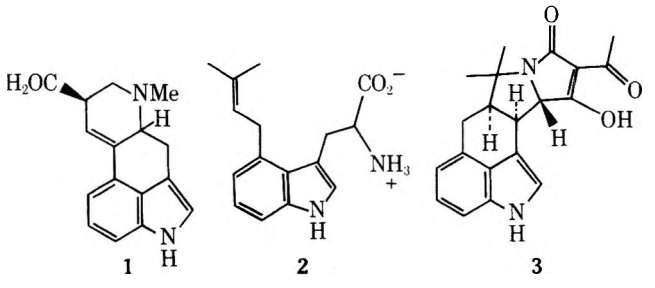
Treatment of 2,3,3-trimethyl-4-pentenal phenylhydrazone in refluxing ethylene glycol led to 1-(3-methylbut-2-en-1-yl)-3-methylindole, presumably through allylic rearrangement to the indolic nitrogen of the intermediate 3-(1,1-dimethylallyl)-3-methylindolenine; no rearrangement to a 4-allylindole derivative was observed. Treatment of 1,3-cyclohexanedione-2-chloro-6-(3-methylbut-2-en-1-yl) phenylhydrazone in refluxing *o*-dichlorobenzene led to 5-allyl-7-chloro indole derivatives, while in aqueous sulfuric acid a 4-alkyl-7-chloro indole derivative was obtained. These derivatives presumably arise via rearrangement of a C-3a isoprenylated intermediate. The formation of these products is discussed in relation to ergot alkaloid biosynthesis.

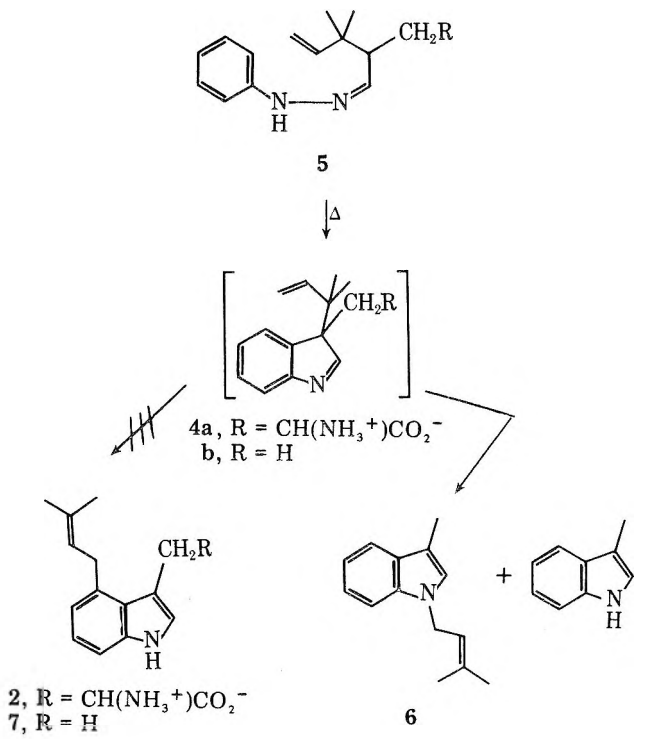
The biosynthesis of lysergic acid (**1**) proceeds from L-tryptophan[1] and mevalonic acid.[2] Recently, an enzyme, dimethylallyltryptophan synthetase,[3] has been isolated which directly forms **2** by coupling L-tryptophan with dimethylallyl pyrophosphate. A related alkaloid, cyclopiazonic acid (**3**), has been shown to derive from a C-4 isoprenylation of a tryptophan derivative.[4] Since such C-4 alkylations are without precedent in the chemistry of indoles, we undertook a study of some chemical model systems for this process.



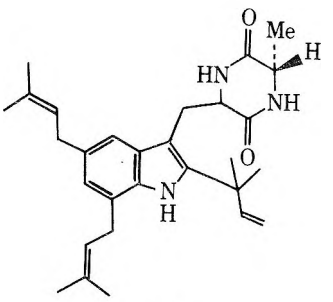
1 2 3

Two hypotheses seemed to offer reasonable chemical explanations for an overall C-4 alkylation during the enzymic reaction. These involved a preliminary conversion of tryptophan to the C-3 substituted derivative, as **4a**, which could undergo subsequent [3,3]-sigmatropic rearrangement to **2** (Scheme I). An alternative is a sequential indoline formation, as **12**, from tryptophan and its direct isoprenylation at C-3a (Scheme III) to **13** followed by a [1,2] shift, thereby establishing the requisite 4-isoprenylated substitution. It is of interest that in this latter scheme isoprenylation of the indoline

Scheme I



12 at the two alternative activated positions, i.e., C-5 and C-7, gives the substitution pattern found in echinulin (14).

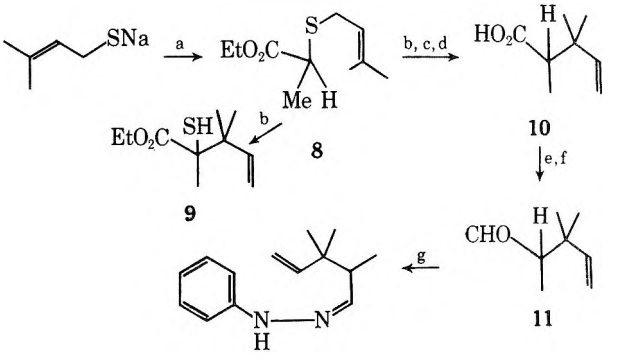


14

To test the first of these possibilities, we generated **4b,** in situ, by the Fischer cyclization of the hydrazone **5.** The well-documented[5] acid sensitivity of 3-allyl-3-alkylindolenines, rearranging to 2,3-disubstituted indoles, prompted our choice of nonacidic conditions. Such noncatalyzed Fischer indole cyclizations have been reported[6] and we found refluxing ethylene glycol to be satisfactory. However, at 198 °C the rearrangement took an unexpected course resulting in the isolation of the known[7] *N*-dimethylallyl-3-methylindole (**6,** 9%) as well as skatole (4%), as the only indolic products. None of the desired 4-substituted **7** was obtained upon chromatography of the crude reaction mixture. Since indole **7** would be expected to survive both the reaction conditions as well as chromatographic workup, the failure to observe **7** implies that indolenine **4b** rearranged preferentially outside the benzenoid system.[8] The formation of skatole probably occurs by thermal elimination of isoprene from **4b.**

The synthesis of hydrazone **5** was achieved in four steps from ethyl α-bromopropionate and is outlined in Scheme II. Sulfide **8** underwent [2,3]-sigmatropic rearrangement[9] when treated with lithium diisopropylamide; however, the resulting thiol **9** could not be cleanly desulfurized with Raney nickel. However, methylation of the thiolate anion followed by desulfurization of the resultant thioether with sodium ethanethiolate[10] proceeded with accompanying cleavage of

Scheme II

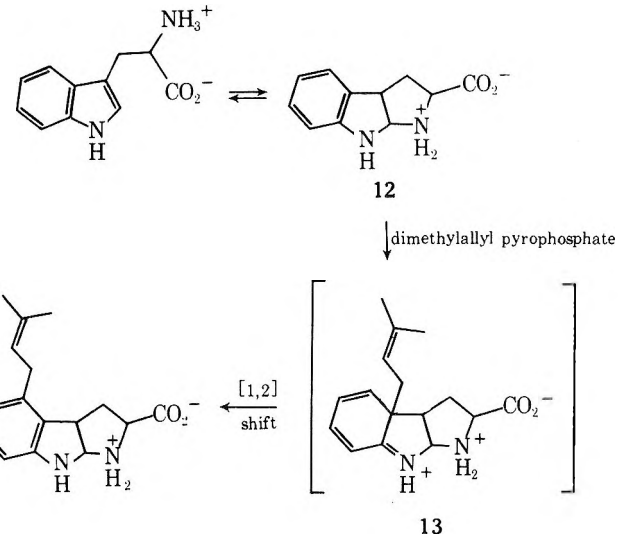


a, ethyl α-bromopropionate, EtOH; b, LDA, THF; c, MeI; d, EtSNa, HMPA; e, $LiAlH_4$; f, $CrO_3 \cdot 2Py$, CH_2Cl_2; g, phenylhydrazine, MeOH.

the ester, to yield acid **10** as a colorless liquid (80% from the thioether). Lithium aluminum hydride reduction and selective reoxidation gave the aldehyde **11** in 9% overall yield from ethyl α-bromopropionate.

The failure of this first possibility led us to explore routes for the in situ generation of C-3a substituted indoles to evaluate the possibility of their [1,2] rearrangement to 4-isoprenylated derivatives. As a reasonable path to an intermediate

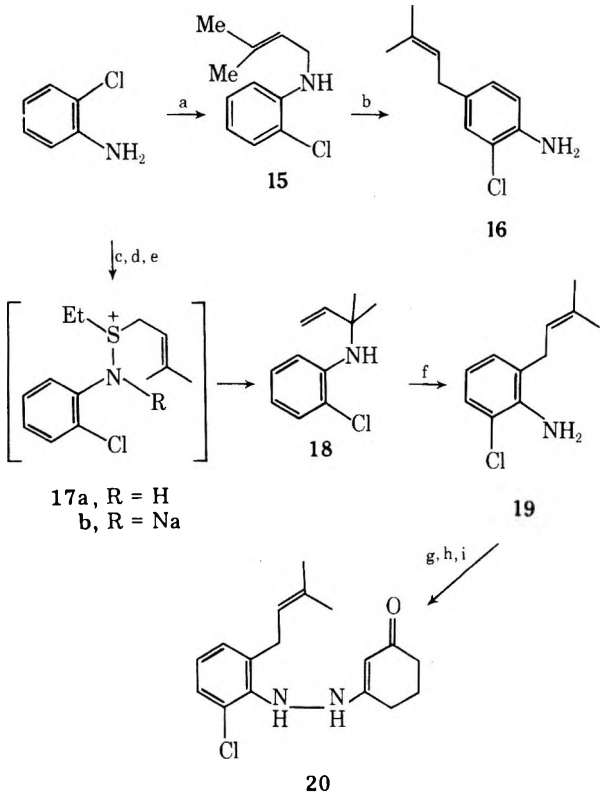
Scheme III



such as **13,** we considered a Fischer cyclization, on the stable enehydrazine **20,** Scheme V.

To this end, we examined possible routes to the aniline **19.** Previous reports by Hurd and Jenkins[11] established that zinc chloride in refluxing xylene caused clean [1,3]-sigmatropic rearrangement of *N*-allylanilines to the ortho-substituted derivatives. Following their method with *N*-allyl-2-chloroaniline only starting material was recovered after 3 h. Therefore, 2-chloro-*N*-(3,3-dimethylallyl)aniline (**15**) was prepared and refluxed in benzene with aluminum chloride to yield the unexpected para-substituted aniline **16.** The substitution pattern was assigned on the basis of the ^1H NMR spectrum by comparison with that of 2-chloro-4-methylaniline. As an alternative, Gassman[12] had reported specific ortho alkylations of aromatic amines via sulfonium salts such as **17a.** Following his procedure we generated **17a** by treating 2-chloroaniline with *tert*-butyl hypochlorite followed by 3,3-dimethylallyl ethyl sulfide. However, upon treatment with sodium methoxide in methanol the inverted *N*-allylaniline **18** was obtained. This result may be rationalized as proceeding

Scheme IV



a, dimethylallyl bromide
b, $AlCl_3$
c, *tert*-butyl hypochlorite
d, ethyl dimethylallyl sulfide
e, sodium methoxide
f, 1.0 N ethanolic HCl
g, NOCl, THF, −78 °C
h, $LiAlH_4$
i, 1,3-cyclohexanedione

through ylide formation (e.g., **17b**) followed by [2,3]-sigmatropic rearrangement with concomitant desulfurization of the sulfenamide. Similar rearrangements have been reported[13] upon treatment of allylic sulfides with Chloramine-T. Aniline **18** underwent an extremely mild amino-Claisen rearrangement to **19** upon prolonged treatment with ethanolic hydrochloric acid at 25 °C. Conversion to **19** appeared quantitative by NMR analysis after 85 h. Recently, other workers have reported a similar rearrangement at 80 °C.[14]

Since normal conditions for diazotization led to acid-catalyzed ring closure to a tetrahydroquinoline, nitrosyl chloride at −78 °C was found necessary. Reduction of the diazotized amine with lithium aluminum hydride gave a crude hydrazine which proved difficult to purify. A crystalline hydrazone was obtained (32% from aniline **19**) by direct coupling with 1,3-cyclohexanedione and appeared (NMR) to exist in solution exclusiely as the enehydrazine tautomer **20.**

Attempts at Fischer cyclization of enehydrazine **20** under a variety of acidic conditions gave complex mixtures which were difficult to separate. However, by refluxing in aqueous sulfuric acid 8-chloro-1,2,3,4-tetrahydro-4-oxocarbazole **23** (4%) and oxocarbazole **24** (2%) were obtained. Deallylated **23** could arise by thermal elimination of isoprene from intermediate **21** (Scheme V) while the rearranged **24** presumably results from hydration, followed by 1,2 shift of the resulting alkyl group. Such 1,2 shifts of a methyl group have been observed previously upon cyclization of cyclohexanone mesitylhydrazone[15] and more recently a similar shift of a phenyl group has been reported.[16] Attempts to provoke a thermal rearrangement of **20** by refluxing in xylene led to a substantial amount of unreacted starting material after 7 h. However, refluxing *o*-dichlorobenzene gave rapid decomposition and in 25 min three new crystalline carbazoles, **25, 26,** and **27** along with **23,** were isolated by chromatography.

The structural assignments were based on the ^1H NMR spectra (Table I). In these spectra the 4-oxo substituent causes a characteristic downfield shift of H-5, which is useful in determining the substitution pattern. Deallylated carbazole **23** was identical with an authentic sample, prepared using *o*-chloroaniline.

These products are best understood as arising from an initial Fischer cyclization of **20** to a pair of isomeric pyrollines **21** and **22.** Acid-catalyzed rearrangement and hydration gives **23** and **24,** while the thermal pathway from **21** leads by way of [3,3]- and [1,3]-sigmatropic shifts to **25** and **26.** Such competing [3,3] and [1,3] shifts have been observed previously[17] and have been associated with radical dissociation–recombination pathways. Such a pathway would also readily explain the presence of deallylated carbazole **23.** In contrast, dechlorination of **22** leads to carbazole **27.**

Scheme V

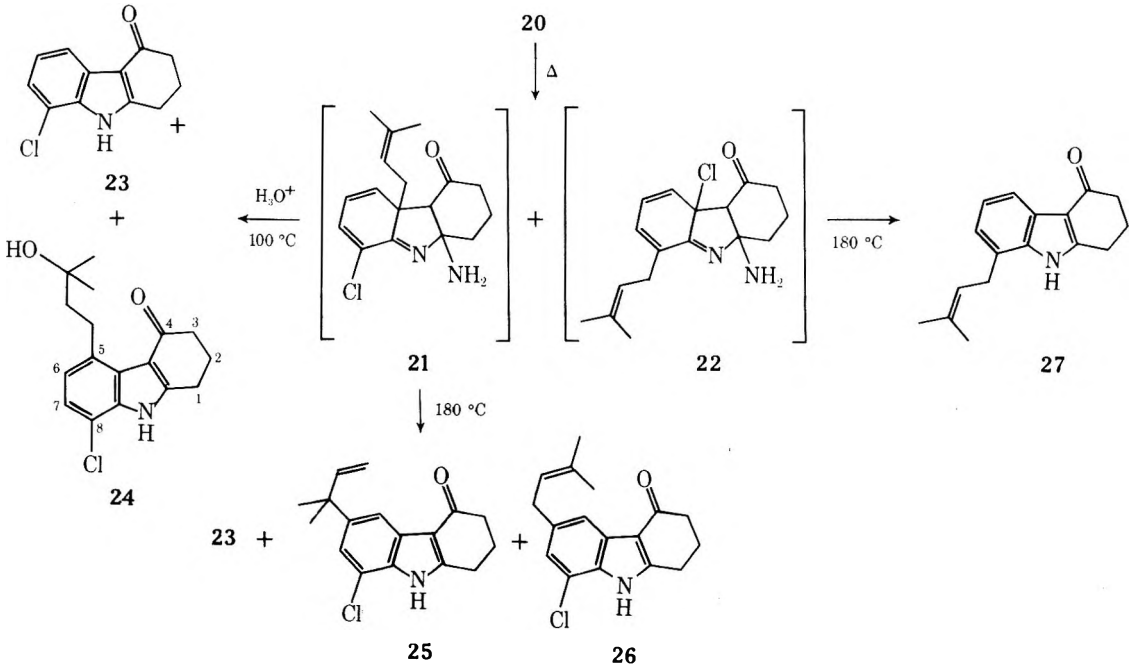


Table I[a]

Carbazole	H_5	H_6	H_7	Mp, °C	Yield, %
24[b]		6.92	7.16	180–181	2
5-alkyl, 8-chloro		AB quartet	J = 8		
25[c]	8.00		7.13	278–279.5	4
6-allyl, 8-chloro	d J = 1.5		d J = 1.5		
23[c]	8.01 d of d	7.29–7.11 complex multiplet		252–256	10[d]
8-chloro	J = 6.0, 2.0				
26[c]	8.03 d J = 1.5		6.98 d J = 1.5	244–246	2
6-allyl, 8-chloro					
27[c]	7.92 d of d	7.09 d of d	6.97 d of d	194–196	5
8-allyl	J = 7.0, 1.75	J = 7.0, 7.0	J = 7.0, 1.75		

[a] The chemical shifts are relative to internal Me_4Si (δ) and all coupling constants are in hertz. [b] Spectrum recorded in Me_2SO-d_6. [c] Spectrum recorded in acetone-d_6. [d] This yield was obtained in refluxing dichlorobenzene.

In summary, these studies show that 3a-dimethylallylated indoles such as **21** do undergo rearrangement to ring substituted derivatives. At high temperatures in neutral media they proceed to 5-substituted products by processes of the [3,3]- and [1,3]-sigmatropic type, which have ample precedent. In acid we have observed a 4-substituted product, **24**, presumably resulting from a [1,2] shift.

Whether such reactions may be useful in making 4-substituted indoles and whether such intermediates are involved in lysergic acid biosynthesis must await further studies.

Experimental Section

Melting points were determined on a Kofler hot stage microscope or Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Midwest Microlabs Inc., Indianapolis, Ind., or Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on a Hitachi Perkin-Elmer R-22B instrument or Varian Associated T-60 spectrometer. Silica gel for column chromatography was Merck silica gel 60, no. 7734, or Merck silica gel H type 60, no. 7736. NMR values are expressed in δ downfield from internal Me_4Si while UV maxima are expressed in nanometers.

1-(3-Methyl-2-butenyl)-3-methylindole (6).[7] Indole **6** was prepared by a modification of the literature procedure using HMPA instead of DMF as the solvent. **6** was obtained as a colorless liquid (47%), bp 86 °C (0.075 mm).

Indolization of Hydrazone 5. A solution of hydrazone **5** (1.0 g, 4.62 mmol) in dry ethylene glycol (10 mL) was refluxed under a nitrogen atmosphere for 5.5 h. The cooled reaction mixture was diluted with water (50 mL and extracted with ether. Normal workup and evaporation gave 660 mg of a brown oil.

Column chromatography on silica gel (50 g) eluting with benzene gave indole **6** as a colorless liquid, 78 mg (9%): mass spectrum (70 eV) M^+ m/e 199; the IR and NMR spectra were superimposable upon those obtained from an authentic sample prepared by a published procedure.[7]

Skatole eluted next and was obtained as a white solid, 25 mg (4%), mp 94–95 °C.

Continued elution with a benzene–ethyl acetate gradient led to intractable brown tars which proved difficult to characterize.

α-Carboethoxyethyl 3-Methyl-2-butenyl Sulfide (8). 3-Methyl-2-butenethiol (18.4 g, 180 mmol) in absolute ethanol (10 mL) was added dropwise, under N_2 and with stirring, to a precooled (0 °C) solution of sodium ethoxide (180 mmol) in ethanol (200 mL), and the resulting solution was stirred at 25 °C for 10 min. To the above solution was added dropwise ethyl α-bromopropionate (32.6 g, 180 mmol) as a solution in absolute ethanol (100 mL), and the resulting suspension was stirred at 25 °C for 3 h. The sodium bromide precipitate was filtered and the filtrate was evaporated to leave crude **8**, 35 g (96%), a colorless liquid. Bulb to bulb distillation at an oven temperature of 52 °C (0.15 mm) gave water-white **8**, 23 g (63%): IR (neat) 1732 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (3, t, J = 7 Hz, ester Me), 1.45 (3, d, J = 7 Hz, secondary methyl), 1.75 (3, br s, vinyl methyl), 1.78 (3, br s, vinyl methyl), 3.3 (3, m, methylene and methine), 4.20 (2, q, J = 7 Hz), 5.24 (1, t, J = 8 Hz, vinyl H).

2-Carboethoxy-3,3-dimethyl-4-pentene-2-thiol (9). To a cold (0 °C) solution of lithium diisopropylamide (21.4 mmol) in dry THF (25 mL) was added under nitrogen sulfide **8** (2.88 g, 14.2 mmol), and the mixture was allowed to warm to 23 °C with stirring continued for 3 h. Evaporation of the solvent left an oil which was taken up in ether, washed with H_2O and brine, dried ($MgSO_4$), and evaporated to leave crude thiol **9** (2.75 g, 96%) in at least 95% purity as judged by ^1H NMR: bp 95 °C (3 mm) (bulb to bulb); IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$) 1.20 (6, s, *gem*-dimethyl), 1.30 (3, t, J = 7 Hz, ester Me), 1.48 [3, d, J = 1 Hz, collapses to singlet with D_2O, (R)(R[1]) (SH) **Me**], 2.32 (1, br s, exchanges with D_2O, –SH), 4.2 (2, q, J = 7 Hz, CO_2CH_2–), 4.85–5.35 (2, m, vinyl methylene), 6.06 (1, d of d, J = 10, 19 Hz, vinyl H); mass spectrum (70 eV) M^+ m/e 202. Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.96. Found C, 59.85; H, 9.01.

2,3,3,-Trimethyl-4-pentenoic Acid (10). To a cold (0 °C) solution of lithium diisopropylamide (260 mmol) in dry THF (150 mL) was added dropwise sulfide **8** (35 g, 173 mmol) as a solution in THF (300 mL) under nitrogen. After the addition was completed the red reaction mixture was first warmed to room temperature and stirre for an additional 30 min, then treated dropwise with methyl iodide (37 g, 260 mmol) and stirred for 3 h at 25 °C. Evaporation of the THF left a red oil which was dissolved in ether, washed with water and brine, dried ($MgSO_4$), and evaporated. Distillation afforded a pale yellow liquid, 14.8 g (39%), bp 84–86 °C (1.7–2.2 mm), identified as the rearranged thioether by its spectral properties: IR (neat) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (6, s, *gem*-dimethyl), 1.33 (3, t, J = 7 Hz, CH_2CH_3), 1.50 (3, s, tertiary methyl), 2.02 (3, s, SCH_3), 4.17 (2, q, J = 7 Hz), 5.10 (2, m, vinyl CH_2), 6.07 (1, d of d, J = 18, 10 Hz, vinyl CH).

Ester hydrolysis was found to accompany desulfurization.[10] The thioether above (5.0 g, 23.1 mmol) was heated at 85 °C with an excess of sodium ethanethiolate (9.7 g, 120 mmol, 5 equiv) in dry HMPA under nitrogen for 2.5 h. The cooled reaction mixture was poured into 0.1 M aqueous HCl and extracted with ether. The ethereal extract was washed exhaustively with water and brine, dried ($MgSO_4$), and evaporated to leave acid **10** as a pale yellow liquid, 2.6 g (80%): IR (neat) 3450–2450 (br), 1710 cm^{-1}; NMR ($CDCl_3$) 1.13 (6, s, *gem*-dimethyl), 1.14 (3, d, J = 7 Hz, secondary CH_3), 2.52 (1, q, J = 7 Hz, methine), 5.15–4.75 (2, m, vinyl CH_2), 5.87 (1, d of d, J = 18, 9 Hz, vinyl H), 10.4 (1, br s, exchanges in D_2O, $-CO_2H$).

2,3,3-Trimethylpent-4-en-1-ol. To a suspension (0 °C) of lithium aluminum hydride (995 mg, 26.1 mmol) in dry ether (25 mL) was added dropwise under nitrogen 2,3,3-trimethylpent-4-enoic acid (3.5 g, 25 mmol) in dry ether. After the addition had been complete, the reaction was stirred at 25 °C for 10 h. Water (6 mL) was added and the resulting precipitate filtered and washed with ether. Normal workup and evaporation gave a yellow oil which was distilled to afford 2,3,3-trimethylpent-4-en-1-ol, 2.37 g (74%): bp 89–94 °C (25 mm); IR (neat) 3350 (br), 1040, 930 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3, d, J = 6 Hz, methyl), 1.03 (6, s, *gem*-dimethyl), 1.42 (1, m, methine), 1.73 (1, s, exchanges with D_2O, OH), 3.30 (1, d of d, J_{gem} = 9, J_{vic} = 7 Hz, CH_2OH), 3.75 (1, d of d, J_{gem} = 9, J_{vic} = 5 Hz, CH_2OH), 4.70–5.08 (2, m, vinyl CH_2), 5.82 (1, d of d, J = 18, 9 Hz, vinyl H).

2,3,3-Trimethyl-4-pentenal Phenylhydrazone (5). To a solution of CrO_3-2pyridine (160 mmol) in methylene chloride[18] (400 mL) was added 2,3,3-trimethyl-4-pentenol (3.42 g, 26.8 mmol) as a solution in methylene chloride (7 mL) and the resultant black suspension was stirred at 25 °C for 15 min. The methylene chloride solution was decanted from the black precipitate and washed with 10% NaOH, 1 N HCl, saturated $NaHCO_3$, and brine, then dried ($MgSO_4$) and evaporated to leave **11**, 2.28 g (68%), as a colorless liquid: IR (neat) 1720, 2750 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (3, d, J = 7 Hz, secondary CH_3), 1.15 (6, s, *gem*-dimethyl), 2.24 (1, d of q, J = 7, 2 Hz, methine), 5.10–4.73

(2, m, vinyl methylene), 5.80 (1, m, vinyl H), 9.70 (1, d, J = 2 Hz, CHO).

Aldehyde **11** gave the phenylhydrazone **5** as a colorless oil (89%): bp 105 °C (0.35 mm) (Kugelrohr); IR (neat) 3310, 1601, 1510, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (6, s, *gem*-dimethyl), 1.07 (3, d, J = 7 Hz, Me), 2.26 (1, q, J = 7 Hz, methine), 4.77–5.13 (2, complex m, vinyl CH_2), 5.60–6.13 (1, complex m, vinyl H), 6.63–7.42 (7, complex m, ArH, NH, N=CHR); mass spectrum (70 eV) M^+ *m/e* 216.

***N*-(3,3-Dimethylallyl)-2-chloroaniline (15).** To mechanically stirred ice-cold o-chloroaniline (71.9 g, 562 mmol) was added dropwise dimethylallyl bromide (41.85 g, 281 mmol) as a solution in dry ether (50 mL), under nitrogen. After the addition was complete, the mixture was allowed to warm to 25 °C and stirred for 16 h, the resulting suspension was diluted with ether and filtered, and the precipitate was washed with ether. The orange ethereal solution was washed with 10% NaOH and brine, dried (Na_2SO_4), and evaporated to leave 62 g of an oil. The oil was distilled through Vigreux and gave two fractions. The higher boiling was a colorless liquid, 30.8 g, bp 76–79 °C (0.15–0.25 mm), and this fraction was redistilled through Vigreux (10 cm) to give the *N*-allylaniline **15** as a colorless liquid, 24.5 (46%): bp 58–60 °C (0.04 mm); IR (neat) 3420, 1601, 1520, 765 cm^{-1}; NMR ($CDCl_3$) δ 7.36–6.52 (4, complex m, ArH), 5.36 (1, t, J = 6 Hz, vinyl H), 4.22 (1, br s, exchanges with D_2O), 3.72 (2, d, J = 6 Hz, methylene), 1.76 (3, d, J = 0.4 Hz, vinyl methyl, 1.73 (3, br s, vinyl methyl).

2-Chloro-4-(3,3-dimethylallyl)aniline (16). To a suspension of aluminum chloride (6.78 g, 51 mmol) in dry benzene (50 mL) was added a solution of **15** (10 g, 51 mmol) in dry benzene (100 mL) (a pale yellow solution developed) and then the solution was refluxed for 15 h. Upon cooling, the black precipitate was digested with 50% KOH (300 mL) and the aqueous phase extracted with ether. After normal workup and evaporation, the resultant oil was chromatographed on silica (80 g). Benzene (400 mL) elution gave a crude fraction (2.62 g) containing starting material and desired product. Distillation afforded **16** as a colorless liquid, 1.0 g (10%): bp 86–87 °C (0.04 mm); NMR ($CDCl_3$) δ 7.30–6.58 (3, complex m, ArH), 5.22 (1, t, J = 7 Hz, vinyl H), 3.83 (2, s, NH_2), 3.70 (2, d, J = 7 Hz, CH_2), 1.73 (3, br s, vinyl methyl), 1.70 (3, br s, vinyl methyl). The aromatic region was identical with that of an authentic sample of 2-chloro-4-methylaniline.

***N*-(1,1-Dimethylallyl)-2-chloroaniline (18).** To a solution of *o*-chloroaniline (59.1 g, 462 mmol) in dry methylene chloride (600 mL) at −78 °C was added, under $_2$, *tert*-butyl hypochlorite (55.3 mL, 462 mmol) as a solution in methylene chloride (500 mL). After stirring at −78 °C for 30 min a methylene chloride (300 mL) solution of 3,3-dimethylallyl ethyl sulfide (60 g, 462 mmol) was added dropwise under N_2. After stirring for an additional 30 min, the resulting black mixture was treated with sodium methoxide in methanol (462 mmol, 300 mL) and stirring was continued for an additional 15 min at −78 °C; then the mixture was allowed to warm to room temperature and stirred overnight. The resulting red-black mixture was washed with water and brine, then dried (Na_2SO_4) and evaporated to a black liquid. Distillation through Vigreux (10 cm) gave *N*-(1,1-dimethylallyl)-2-chloroaniline (**18**, 64.4 g, 77%) as a pale yellow liquid: bp 84–89 °C (1.9–2.0 mm); IR (film) 3400, 1598, 1510, 1470, 1330, 1200, 1045, 930, 755 cm^{-1}; NMR ($CDCl_3$) δ 7.38–6.45 (4, complex m, ArH), 6.04 (1, d of d, J = 18, 10 Hz, vinyl H), 5.15 (1, d of d, J = 18, 2 Hz, vinyl H), 5.10 (1, d of d, J = 10, 2 Hz, vinyl H), 4.6–4.35 (1, br, NH exchangeable in D_2O), 1.42 (6, s, *gem*-dimethyl).

6-Chloro-2-(3,3-dimethylallyl)aniline (19). *N*-(1,1-Dimethylallyl)-2-chloroaniline (10.2 g, 52 mmol) was stirred at 25 °C with 1.0 N ethanolic hydrochloric acid (77 mL, 77 mmol) for 85 h. The mixture was neutralized with bicarbonate and extracted with methylene chloride, and the organics were washed with brine, dried (Na_2SO_4), and evaporated to leave 10.1 g of a pale yellow liquid. An NMR spectrum of this crude material indicates that complete conversion had occurred. Distillation through Vigreux gave **19** as a colorless liquid, 6.5 g (64%): bp 84–96 °C (0.1 mm); IR (film) 3452, 3360, 1605, 1485 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (1, d of d, J = 7, 2 Hz, ArH), 6.97 (1, d of d, J = 7, 2 Hz, ArH), 6.63 (1, d of d, J = 7, 7 Hz, ArH), 5.21 (1, t, J = 7 Hz, vinyl H), 4.40–3.55 (2, br s, exchanges with D_2O, NH_2), 3.23 (2, d, J = 7 Hz, CH_2), 1.74 (6, br s, vinyl methyls).

1,3-Cyclohexanedione 2-Chloro-6-dimethylallyl Phenylhydrazone (20). To a solution of 2-chloro-6-dimethylallylaniline (2.45 g, 12.5 mmol) and dry pyridine (1.01 mL, 12.5 mmol) in dry THF (150 mL) at −78 °C and under nitrogen was added nitrosyl chloride in methylene chloride (9.0 mL, 1.44 M, excess), slowly with care being taken to maintain the temperature below −65 °C during the addition. After stirring at −70 °C for 30 min, $LiAlH_4$ (950 mg, 25 mmol) was added slowly, maintaining the temperature below −60 °C during addition. The mixture was stirred at −70 °C for 30 min and allowed to warm to 25 °C with stirring continued for 1 h. The resulting mixture was cooled in an ice bath, treated sequentially with water (1 mL), 10% hydroxide (2 mL), and water (3 mL), and then stirred for 4 h. The white precipitate was filtered and washed with ether,and the combined organics were dried (Na_2SO_4) and evaporated to a yellow liquid (2.35 g).

A solution of cyclohexane-1,3-dione (1.40 g, 12.5 mmol) in methanol (20 mL) was added to the yellow liquid above (2.35 g) in methanol (10 mL), and the resulting solution was stirred overnight under N_2. Evaporation of the methanol left a red oil, which was taken up in methylene chloride and washed with brine, dried (Na_2SO_4), and evaporated to leave a red oil (3.6 g). The enehydrazine was obtained as an oily semisolid after chromatography on silica gel H (400 g) with ethyl acetate elution. The enehydrazine **20** was crystallized from ether–hexane as yellow crystals, 1.21 g (32%): mp 110–110.5 °C; IR ($CHCl_3$) 3350, 3400–3200, 1712, 1580 cm^{-1}; NMR ($CDCl_3$) δ 8.7–7.6 (1, br s, exchanges in D_2O, ArNH), 7.17–6.95 (2, complex m, ArH), 6.86 (1, d of d, J = 7, 7 Hz, *p*-ArH), 5.96 (1, br s, exchanges, NH), 5.57 (1, s enol H), 5.21 (1, br t, J = 7 Hz, vinyl H), 3.26 (2, d, J = 7 Hz, CH_2), 2.65–1.60 (6, m, ring protons), 1.72 (3, s, vinyl methyl), 1.63 (3, s, vinyl methyl); UV (EtOH) λ_{max} (log ϵ) 295 nm (4.38); MS (70 eV) *m/e* 304 (M^+), 306 ($M + 2^+$).

Anal. Calcd for $C_{17}H_{21}Cl_1N_2O$: C, 66.98; H, 6.95; N, 9.12. Found: C, 67.04; H, 6.98; N, 9.04.

1,3-Cyclohexanedione Mono-2-chlorophenylhydrazone. To a refluxing solution of 2-chlorophenylhydrazine hydrochloride (3.38 g, 18.9 mmol) in absolute ethanol (25 mL) was added 1,3-cyclohexanedione (2.18 g, 18.9 mmol) as a solution in absolute ethanol (50 mL). The mixture was refluxed for 10 min, diluted with water, and cooled to give a red solid. Recrystallization from aqueous ethanol gave an orange hydrazone, 2.35 g (53%): mp 185–187 °C; NMR (Me_2SO-d_6) δ 1.75–2.80 (6, m, ring methylene), 4.4–5.6 (1, v br s, exchanges in D_2O, NH), 5.50 (1, s, enol H), 6.58–7.40 (4, m, Ar H), 7.95–8.42 (1, br s, exchanges in D_2O, NH).

8-Chloro-1,2,3,4-tetrahydro-4-oxocarbazole (23). A suspension of 1,3-cyclohexanedione 2-chlorophenylhydrazone (1.50 g, 6.36 mmol) in 20% aqueous H_2SO_4 (150 mL) was heated at reflux (125 °C bath) for 5 h. The cooled reaction mixture was diluted with water and extracted with ethyl acetate. Washing of the organic solution with bicarbonate and brine and drying over Na_2SO_4 gave a brown solid after evaporation. Trituration with carbon tetrachloride left a green solid which was recrystallized from acetonitrile five times to give analytically pure **23**, 79 mg (6%): mp 252–256 °C; IR ($CHCl_3$) 3425, 1650, 1470 cm^{-1}; NMR (acetone-d_6) 2.36–2.11 (2, m, ring methylene), 2.49 (2, t, J = 6 Hz, ring methylene), 3.08 (2, t, J = 6 Hz, ring methylene), 7.29–7.11 (2, complex m, Ar H_6 + H_7), 8.01 (1, d of d, J = 6, 2 Hz, Ar H_5); UV (EtOH) λ_{max} (log ϵ) 243 nm (4.16), 265 (4.09), 297 (4.01) shifted to267 (4.40), 327 (4.30) upon addition of hydroxide.

Anal. Calcd for $C_{12}H_{10}NOCl$: C, 65.61; H, 4.59. Found C, 65.46; H, 4.62.

8-Chloro-5-(3-hydroxy-3-methylbutyl)-4-keto-1,2,3,4-tetrahydrocarbazole (24). A degassed solution of the enehydrazine **20** (200 mg, 656 mmol) in aqueous H_2SO_4 (11 mL, 1.64 M, 18 mmol) was heated gently at 102 °C for 15 min. Upon cooling the mixture was diluted with water (100 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated to leave 44 mg. Preparative TLC elution with ether gave a fraction at R_f 0.32–0.27, 6 mg (4%), identified as the deallylated carbazole **23** by its chromatographic and spectral properties.

A second fraction at R_f 0.16–0.19 provided 5 mg which upon crystallization gave **24** as white needles, 4 mg (2%): mp 180–181 °C; IR ($CHCl_3$) 3550–3325, 3420, 1645, 1460 cm^{-1}; NMR (Me_2SO-d_6) 7.16, 6.92 (2, AB q, J = 8 Hz, ArH), 3.02 (2, t, J = 7 Hz, CH_2), 1.19 (6, s, *gem*-dimethyl), the remaining methylene resonances were obscured by D_5 acetone; mol wt ($C_{17}H_{20}NO_2Cl$) calcd 305.11826, found 305.11851.

Thermal Indolization of the Enehydrazine 20. A solution of the enehydrazine **20** (3.37 g, 11.1 mmol) in dry, degassed o-dichlorobenzene (25 mL) was refluxed under nitrogen for 25 min. (The initial suspension dissolves upon warming.) The cooled reaction mixture was concentrated to ca. 12 mL at 25 °C (0.1 mm) to leave a black, viscous liquid. Filtration through a column of silica gel H (75 g) eluting with 50–75% ethyl acetate in hexane gave a mixture of carbazoles as a brown solid (1.5 g). The solid was carefully chromatographed on silica gel H (100 g) using a positive nitrogen pressure.

Elution with ethyl acetate/hexane (1/4) gave carbazole **25**, 132 mg (4%), as white microplates after recrystallization from acetonitrile: mp 278–279.5 °C; NMR (acetone-d_6) 1.47 (6, s, *gem*-dimethyl), 2.58–2.07 (4, m, ring methylene), 3.04 (2, t, J = 6 Hz, ring methylene), 5.14–4.90 (2, m, vinyl methylene), 6.06 (1, d of d, J = 18, 10 Hz, vinyl H), 7.13 (1, d, J = 1.5 Hz, ArH-7), 8.00 (1, d, J = 1.5 Hz, ArH-5); IR

($CHCl_3$) 3430, 1650, 1475 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 247 nm (4.43), 265 (4.24), 293 (4.10), shifted upon addition of 50% NaOH to 327 (4.32), 2.69 (4.41); mol wt calcd for $C_{17}H_{18}ClNO$ 287.10769, found 287.10854. The analytical sample was prepared upon repeated recrystallization from acetonitrile.

Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.99; H, 6.31; N, 4.87. Found: C, 71.07; H, 6.34; N, 4.85.

Continued elution with the same solvent gave carbazole **23**, 230 mg (10%), as colorless needles after recrystallization from acetonitrile, mp 253 –255 °C. The spectral properties were identical with those obtained by the unambiguous route. Continued elution with this same solvent mixture gave carbazole **27**, 135 mg (5%), as colorless needles after recrystallization from acetonitrile: mp 194–196 °C; NMR (acetone-d_6) 1.73 (3, br s, vinyl methyl), 1.76 (3, br s, vinyl methyl), 2.07–2.54 (4, complex m, ring methylene), 3.02 (2, t, J = 6 Hz, ring methylene), 3.57 (2, d, J = 7 Hz, allylic methylene), 5.41 (1, t, J = 7 Hz, vinyl H), 6.97 (1, d of d, J = 7, 1.75 Hz, Ar H_7), 7.09 (1, d of d, J = 7, 7 Hz, Ar H_6), 7.92 (1, d of d, J = 7, 1.75 Hz, Ar H_5), 10.29–10.87 (1, br s, exchanges with D_2O, NH); IR ($CHCl_3$) 3430, 1650, 1470 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 300 nm (4.27), 265 (4.34), 245 (4.43), shifted upon addition of 50% NaOH to 329 (4.43), 268 (4.50); mol wt calcd for $C_{17}H_{19}NO$ 253.14666, found 253.14559. The analytical sample was prepared upon repeated recrystallization from acetonitrile.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.06, H, 7.61; N, 5.50.

Elution with 50% ethyl acetate–hexane gave carbazole **26**, 64 mg (2%), as colorless needles after recrystallization from acetonitrile: mp 244–246 °C, ^1H FT NMR (acetone-d_6) 1.80 (6, br s, vinyl methyl), 2.67–2.13 (4, m, ring methylene), 3.02 (2, t, J = 6 Hz), 3.61 (2, d, J = 7 Hz, allylic methylene), 5.49 (1, br t, vinyl H), 6.98 (1, d, J = 1.5 Hz, Ar H_7), 8.03 (1, d, J = 1.5 Hz, Ar H_5), 10.76–11.36 (1, br s, exchanges with D_2O, NH); IR ($CHCl_3$) 3430, 1650, 1601, 1470 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 295 nm (4.12), 268 (4.25), 248 (4.34), shifted to 328 (4.32), 282 (4.41) upon addition of 50% OH; mol wt calcd for $C_{17}H_{18}ClNO$ 287.10769, found 287.10938.

Continued elution with 50% EtOAc–hexane gave unreacted starting enehydrazine **20** (200 mg) by NMR.

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Registry No.—**5**, 61740-71-4; **6**, 31463-81-7; **8**, 61740-72-5; **9**, 61740-73-6; **9** Me ether, 61740-74-7; **10**, 61740-75-8; **11**, 61740-76-9; **15**, 61740-77-0; **16**, 61740-78-1; **18**, 61740-79-2; **19**, 61740-80-5; **20**, 61740-81-6; **23**, 61740-82-7; **24**, 61740-83-8; **25**, 61740-84-9; **26**, 61740-85-0; **27**; 61740-86-1; skatole, 83-34-1; 3-methyl-2-butenethiol, 5287-45-6; sodium ethoxide, 141-52-6; ethyl α-bromopropionate, 535-11-5; methyl iodide, 74-88-4; sodium ethanethiolate, 811-51-8; 2,3,3-trimethylpent-4-en-1-ol, 30458-03-8; o-chloroaniline, 95-51-2; dimethylallyl bromide, 870-63-3; phenylhydrazine, 100-63-0; 3,3-dimethylallyl ethyl sulfide, 10276-06-9; cyclohexane-1,3-dione, 504-02-9; 2-chlorophenylhydrazine HCl, 41052-75-9; 1,3-cyclohexanedione mono-2-chlorophenylhydrazone, 61740-87-2.

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3-Diazo-4-oxo-3,4-dihydroquinoline. A Novel Synthon for Indole-3-carboxamides

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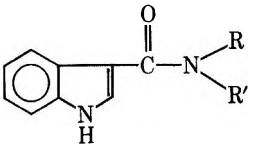
Amides of indole-3-carboxylic acid have been synthesized by a novel reaction employing the ultraviolet irradiation of 3-diazo-4-oxo-3,4-dihydroquinoline in the presence of amines. This diazide, when irradiated, is postulated to undergo an internal Wolff rearrangement to indole-3-ketene which can then add any primary or secondary amine to form the corresponding amide in modest to good yield.

In the past, indole-3-carboxamides have been prepared by the reaction between indole-3-magnesium iodide and *N,N*-dialkylchloroformamides,[1,2] by the dicyclohexylcarbodiimide condensation of aniline with indole-3-carboxylic acid,[3] by the reaction of phenyl isothiocyanate with indole,[4] by the treatment of amines with indole-3-carbonyl chloride,[5] by the reaction of indole with chlorothioformamidinium salts followed by treatment with hydroxides,[6] and by the reductive cyclization of *N,N*-dialkyl-2-(2-nitrophenyl)-2-cyanoacetamides[7] using Pd/C. Most of these syntheses are cumbersome and do not represent a generally applicable synthetic route. On the other hand, it is known that indole derivatives can be obtained from diazoquinolines by photochemical rearrangement. In this manner, 3-diazo-4-oxo-3,4-dihydroquinoline (I) when irradiated in aqueous acetic acid is transformed into indole-3-carboxylic acid.[8]

We have previously shown that when 3-diazo-4-oxo-3,4-dihydroquinoline (I) is irradiated in the presence of an alcohol the corresponding 3-indolecarboxylate ester is formed.[9] We now wish to report that this pathway can also be used as a general route for the synthesis of indole-3-carboxamides. This reported procedure appears to be the simplest one and, to our

Table I



Product[a]	R	R'	% yield	Mp, °C	Mass spectrum, *m/e* (rel intensity)
2	Et	Et	39.4	150.5–151.5	216 (32.8), 144[b] (100), 116 (14.3), 72 (11.4)
3	H	*n*-Butyl	40.0	131–131.5	216 (29.9), 159 (14.9), 144 (100), 116 (14.2)
4	H	Ph	42.0	175[c]	236 (57.4), 144 (100), 93 (32.8), 54 (31.1)
5	H	CH_2Ph	56.4	178	250 (85.4), 144 (100), 106 (18.4)
6	H	CH_2CH_2Ph	58.9	157	264 (20.9), 160 (22.8), 144 (100)
7	H	*o*-ClPh	64.1	209	272 (M^{+2}, 5), 270 (16), 144 (100), 126.9 (18.4)
8	H	*o*-BrPh	49.6	197	315 (12.5), 144 (100)
9	CH_2Ph	CH_2Ph	60.2	187–188	340 (16.9), 249 (36.4), 144 (100)

[a] A satisfactory elemental analysis was obtained for all new compounds. [b] The 144 value corresponds to the acylium ion. [c] Literature value, 173–175 °C.[2]

knowledge, represents the only general synthesis of such compounds. Compounds synthesized by this method are listed in Table I.

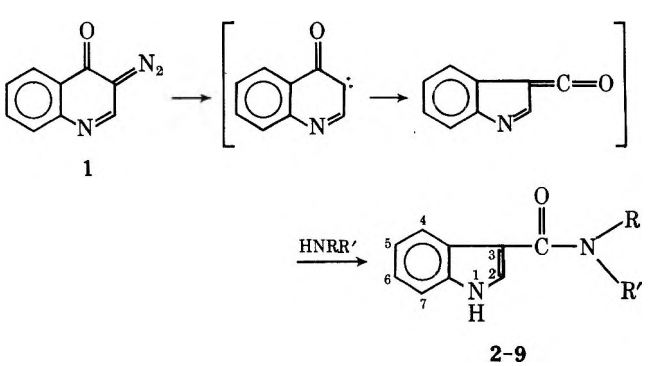
Discussion

All reactions were completed in approximately 6 h. During the course of the reaction, nitrogen, from the diazide photolysis, could be seen bubbling through the solution. The absence of bubbling served in itself as an indication of reaction completion.

Products were identified by their IR and NMR spectra. The classic indole N–H stretch occurred in the IR as a sharp peak from 3450 to 3250 cm^{-1}. The conjugated carbonyl stretch of the secondary amides was found to take place from 1650 to 1610 cm^{-1}, whereas in the tertiary amides it occurred at a lower frequency of 1600 cm^{-1}. In the NMR, an "indole fingerprint" was seen as the 2, 4 + 5 + 6, and 7 proton peak patterns appearing, respectively, as two doublets (J = 3 Hz) (δ 6.8–7.2) and a multiplet (δ 7.8). Mass spectral data show the indole acylium ion (*m/e* 144) as the base peak of all of our compounds.

Although mechanistic investigations are still underway, the reaction appears to proceed via an internal Wolff rearrangement[10] involving the formation of an intermediate carbenoid species which rearranges to the ketene (see Scheme I). This

Scheme I



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2-9

then adds a molecule of amine to form the corresponding amide.

Experimental Section

The following instruments were used: IR (KBr), Hilger & Watts H-1200 Mark II; NMR, Varian EM390 (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad); mass spectra, HP-5982A GC/MS interfaced with an HP-5934A data system. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points (uncorrected) were determined on a Thomas-Hoover capillary melting point apparatus. Silica gel GF_{254} plates (Merck, Germany) were used for thin and thick layer chromatography and were developed in methanol–chloroform (1:9). 3-Diazo-4-oxo-3,4-dihydroquinoline (1) was synthesized from 3-amino-4-hydroxyquinoline hydrochloride[11] which was diazotized according to Süss.[8]

In each reaction, 200 mg (8.55×10^{-1} mmol) of compound 1 was dissolved in 10 mL of methylene chloride (reagent grade) to which 0.5 mL of amine in 2 mL of methylene chloride was added. A little of this solution was set aside in a dark freezer compartment for use as a chromatographic reference standard. Methylene chloride was chosen as the solvent owing to its low boiling point, its availability, and its inert properties. The remaining mixture was transferred to a Pyrex test tube, lightly stoppered, and irradiated with a Hanovia high-pressure mercury vapor lamp until TLC showed the disappearance of starting material.

After irradiation, the reaction mixture was allowed to sit for 0.5 h. Crystals separated from solutions for products **5**, **7–9**, by the end of this period. The crystals were filtered, dissolved in 20 mL of ethanol, and boiled with 0.25 g of Norite. The resulting solution was filtered and 4 mL of water was added to the filtrate. This volume was then reduced under vacuum until crystals were seen to precipitate from solution. For reactions 2–4 and 6, crystals did not appear upon standing. In those cases, the volume of the reaction mixture was reduced under vacuum to 2 mL and the resulting mixture chromatographed on a preparative plate which was developed, dried, and then redeveloped. The UV-quenching band (R_f determined on TLC) was then scraped off and eluted with 100 mL of methanol–chloroform (1:9). All of the elutant was collected in one flask. The solvent was evaporated and the partially purified product was repurified as mentioned above.

The products are listed in Table I together with the physical properties. the IR and NMR spectra of all compounds were consistent with the assigned structure.

Acknowledgments. One of us (J.T.C) was supported by a research fellowship from the Slovenian Research Community, Ljubljana, Yugoslavia, and by a Research Internship from the College of Physical and Mathematical Sciences of Brigham Young University. Dr. E. G. Paul of the Brigham Young University Chemistry Department is thanked for his many discussions of our NMR data.

Registry No.—1, 13240-40-9; 2, 61788-23-6; 3, 61788-24-7; 4, 17954-06-2; 5, 61788-25-8; 6, 61788-26-9; 7, 61788-27-0; 8, 61788-28-1; 9, 61788-29-2; diethylamine, 109-89-7; butylamine, 109-73-9; aniline, 62-53-3; benzylamine, 100-46-9; phenethylamine, 64-04-0; *o*-chlorophenylamine, 95-51-2; *o*-bromophenylamine, 615-36-1; dibenzylamine, 103-49-1.

Supplementary Material Available. Infrared, NMR, and analytical data for compounds 2–9 (2 pages). Ordering information is given on any current masthead page.

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Remote Oxidation in the Fe(II)-Induced Decomposition of a Rigid Epidioxide[1a]

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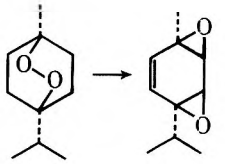
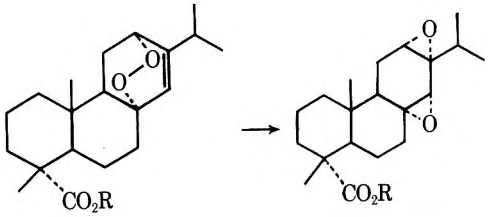
Reaction of the diterpenoid epidioxide **5** with ferrous sulfate gave by remote oxidation the tetrahydrofuran **14a** and the olefin **18a** and by reduction the diol **6**. Structures of **14a** and **18a** were established by a combination of chemical and physical methods and were confirmed by x-ray diffraction of a derivative of **14a**. The mechanism of the Fe(II)-induced remote oxidation of epidioxides which actually involves the Fe(II)–Fe(III) redox system is discussed. The $FeSO_4$–$Cu(OAc)_2$ system also caused remote oxidation in the decomposition of **5**. Highest yields of remote oxidation products were produced by $VO(AcAc)_2$. An unusual isomerization of a 12-chloro derivative of **5** was discovered.

The thermal rearrangement of unsaturated epidioxides to diepoxides, exemplified by the conversion of ascaridole (**1**) to **2**[2,3] and of the epidioxide **3a** of levopimaric acid to **4**,[4] has



1 **2**



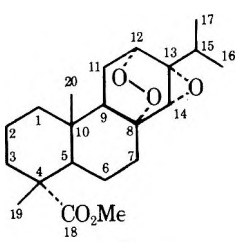
3a, R = H
b, R = Me

4a, R = H
b, R = Me

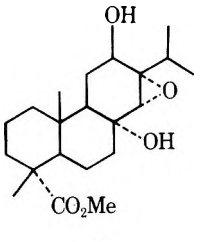
assumed importance not only because of its use in the preparation of the long-elusive arene dioxides and trioxides,[5,6] but also because of the discovery of naturally occurring diepoxides[7-9] and the tumor-inhibitory activity of this functionality.[9] The rearrangement can also be induced photolytically;[10] it is less well known that it can also be effected by ferrous ion at much lower temperatures[11] and that, at least in the case of **3**, this procedure leads to greatly improved yields.

The mechanism proposed for the thermal and photolytic reaction involves homolytic fission of the O–O bond followed by attack of the oxygen atoms on the double bond and cyclization. No mechanism has been proposed for the Fe(II)-induced reaction, but in light of the usual one-electron reduction of the O–O bond by Fe(II),[12] one may conclude that the radical anion chemistry displayed by hydroperoxides and dialkyl peroxides without proximate double bonds is altered to *apparent* diradical chemistry in the unsaturated endoperoxide by oxidation of the initially formed anion radical.

Earlier[13] we had prepared the epoxidic epidioxide **5** from **3b** and were now interested in the behavior of this saturated endoperoxide under the influence of Fe(II). This resulted in approximately equal amounts of diol **6**[13] and two new isomeric



5



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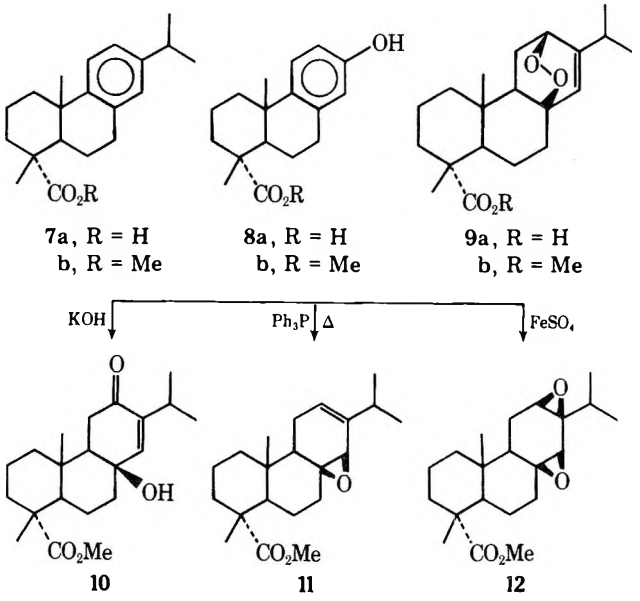
compounds of formula $C_{21}H_{32}O_5$. Structure elucidation of these substances revealed that they had been formed by a new type of remote oxidation reaction. The details of this discovery constitute the subject of this communication.

Results

Preparation of Starting Material. Reaction of sodium levopimarate with singlet oxygen by the original procedure[14] gave variable yields (30–50%) of **3a**; other products which have

not previously been identified were dehydroabietic acid (**7a**, 18%, formed either by disproportionation or dehydration of the 1,4-glycol **6**), the podocarpic isomer **8a** (5%), the diepoxide **4a** (2.5%, presumably the result of thermal rearrangement of **3a** under the reaction conditions), and 2.5% of the new epidioxide **9a**, apparently the first example of a Diels–Alder adduct formed from the more hindered "folded" side of levopimaric acid.[15] The most efficient procedure for the preparation of starting material was reaction of methyl levopimarate with singlet oxygen which furnished 65% of **3b**, 14% of **7b**, and 2% of **9b**. The structure of the new epidioxide **9b** in whose NMR spectrum the C-10 methyl signal exhibited a dramatic downfield shift of 0.64 ppm relative to that of **3b** was established by transformations to **10**, **11**, and **12** which are similar to those previously used for **3b**.[4] In all these substances the C-10 methyl frequency is "normal", instead of being shielded as in derivatives of **3b**.



Reaction of Epidioxide of Methyl Levopimarate with $FeSO_4$. Reaction of **5**[13] with $FeSO_4$ in aqueous tetrahydrofuran gave three substances which were separated chromatographically. The product of medium polarity (31%) was the known diol **6**.[13] The least polar substance A ($C_{21}H_{32}O_5$, 28%) was a hydroxy ester (IR bands at 3545 and 1712 cm^{-1}) which retained the isopropyl group of the starting material (NMR spectrum) as well as the 13,14-epoxide (sharp singlet at 3.28 ppm) and had a new hydroxyl group (presumably α oriented due to the stereochemistry of the starting material) attached to C-12 (multiplet at 4.03 ppm). The fifth oxygen atom of the empirical formula was that of an ether one of whose termini was obviously attached to C-8. The other terminus was assumed to be either C-9 as in **13**, or C-5 as in **14** (Scheme I).

Formation of such a substance could be rationalized by assuming initial cleavage and reduction by Fe(II) of the O–O bond to a radical anion C or D (Scheme I).[12] Abstraction of H-9 by the oxy radical of C (1,3-hydrogen transfer) or D (1,4-hydrogen transfer), oxidation of the radical at C-9 by Fe(III), and combination of the carbonium ion at C-9 with the hydroxyl or oxygen anion at C-8 would have led to **13**. Alternatively, abstraction of H-5 by the oxy radical of C (1,5-hydrogen transfer), oxidation of C-5, and recombination with hydroxyl at C-8 would have led to **14**.

The most polar substance B (33%, $C_{21}H_{32}O_5$) was a dihydroxy ester (IR bands at 3520, 3458, and 1740 cm^{-1}) whose IR spectrum showed retention of the isopropyl group, a singlet at 3.03 ppm typical of H-14 in the various 13,14-epoxides under study, a multiplet at 4.16 ppm attributed to the presence of a hydroxyl group on C-12, and a triplet at 5.67 ppm which indicated the presence of a trisubstituted olefin. Structural possibilities included **16**, formed by deprotonation of a carbonium ion generated from **13** by acid-catalyzed ring

Scheme I

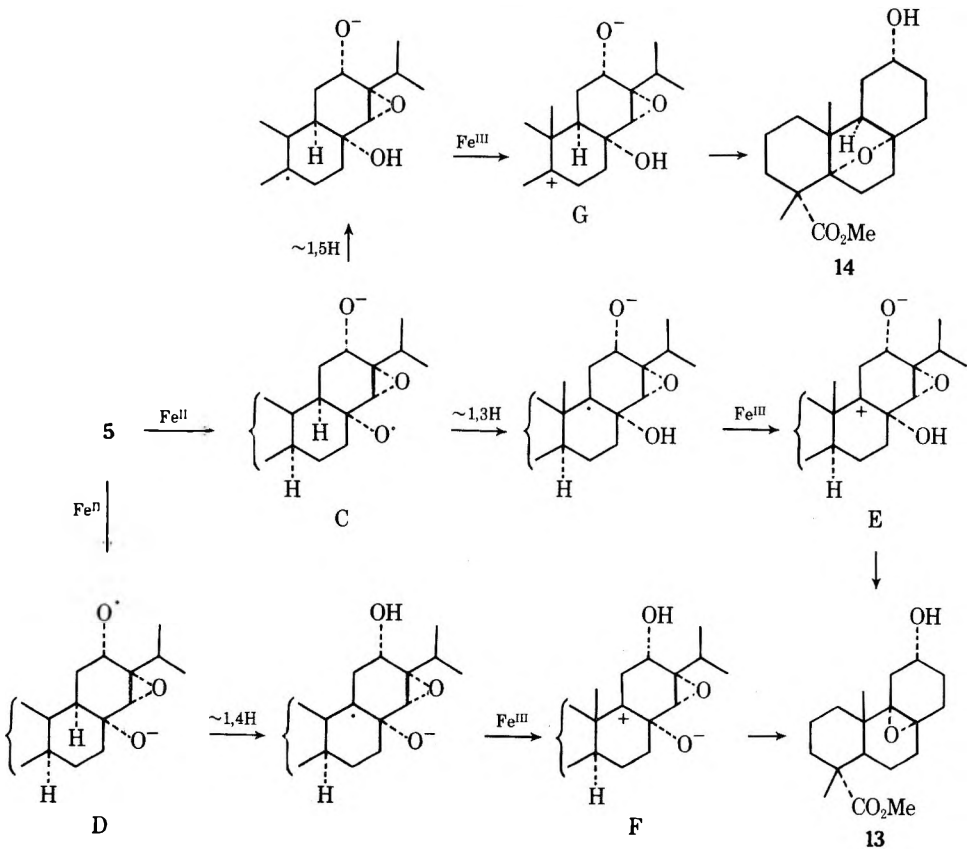
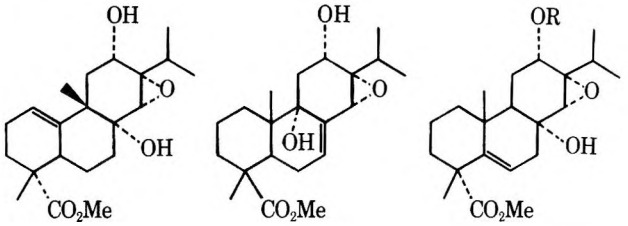


Table I. NMR Spectra of 14a, 21, 22, and 23[a]

Registry no.	Compd	H-12	H-14	H-16,[b] H-17[b]	H-18[b]	H-19[b]
61597-81-7	14a[c]	4.02 m ($W_{1/2}$ = 8.5 Hz)	3.29	0.82 d, 1.01 d (7)	0.97	1.29
61597-82-8	21[c]	4.24 m ($W_{1/2}$ = 18 Hz)	3.37 d (1)	0.83 d, 0.94 d (7)	0.98	1.29
61617-19-4	22[c]	4.38 m ($W_{1/2}$ = 8.5 Hz)	3.26	0.82 d, 1.01 d (7)	0.97	1.29
61617-20-7	23[d]	4.00 m ($W_{1/2}$ = 18 Hz)	3.23 d (1)	0.89 d, 0.92 d (6.5)	0.97	1.27

[a] In $CDCl_3$. Values in parts per million relative to Me_4Si. Coupling constants in hertz. [b] Three protons. [c] At 90 MHz. [d] At 60 MHz.

opening and methyl migration, **17** from **13** by acid-catalyzed ring opening and deprotonation, or **18** by deprotonation of ion G (Scheme I).

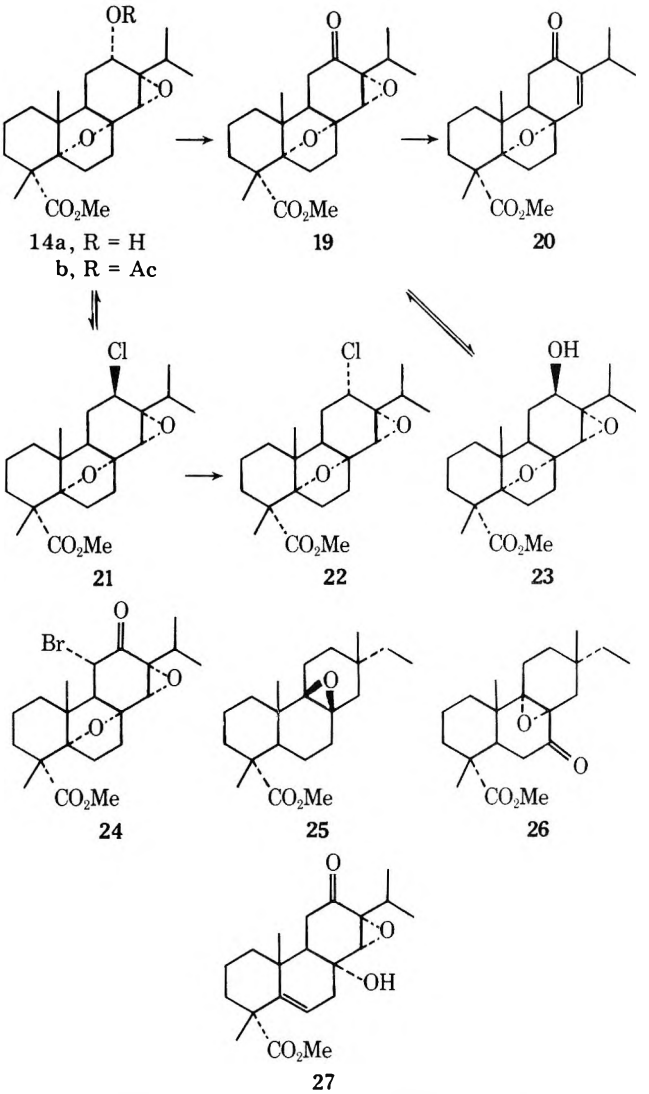


These possibilities were corroborated by the ^{13}C NMR spectrum of B, which displayed five quartets one of which, at 52.5 ppm, corresponded to the methoxyl, five triplets, five doublets one of which, at 119.9 ppm, corresponded to –CH=, and two, at 66.1 and 63.7 ppm, corresponded to C-12 and C-14, and six singlets. Of the latter, a frequency at 178.2 ppm represented the carbonyl group, a signal at 150.3 ppm corresponded to >C=, and two at 78.1 and 68.9 ppm represented C-8 and C-13 (for a fuller discussion of the ^{13}C NMR spectrum see below).

Since 1,5-hydrogen transfer in alkylperoxy radicals is more favorable than 1,4 or 1,3 transfer,[16] since 1,5-hydrogen transfer is predominant in carbon and alkoxy radicals,[17] and since in fact 1,5-hydrogen transfer completely dominates the intramolecular chemistry of radicals in relatively rigid polycyclic systems owing to a combination of the entropy factor and the requirement for collinearity,[17] formulas **14a** and **18a** seemed a priori considerably more plausible for substances A and B produced by the Fe(II)-induced decomposition of **5**. Chemical studies leading to the verification of this hypothesis will now be described; in the discussion we anticipate the final results for the sake of simplicity.

Structural Studies on A. Oxidation of A (**14a**) with Jones reagent afforded **19**, whose IR spectrum indicated the absence of hydroxyl groups, but which retained the epoxide (NMR singlet at 3.53 ppm). Reduction of **19** with chromous chloride yielded an α,β-unsaturated ketone **20** [IR bands at 1728 and 1667 cm^{-1}, narrowly split (1 Hz) doublet at 6.87 ppm characteristic of a proton attached to the β position of an α,β-unsaturated ketone]. Just as in the case of **10**, the splitting of H-14 arose from allylic coupling to H-15 whose signal was a broadened septet at 2.82 ppm; this could be shown by double irradiation experiments.

These observations confirmed the nature of the functional groups at C-12 through C-14 and confirmed that C-8 was quaternary. Subsequent work was directed at dehydration of **14a** since introduction of an 11,12 double bond would result in appearance of H-11 as a doublet of doublets if formula **14a** were correct. In the event, treatment of **14a** with $POCl_3$ or $SOCl_2$ resulted in 91% (respectively 81%) conversion to a chloride **21** (for stereochemistry vide infra). Several attempts to dehydrochlorinate **21** with Li_2CO_3–DMF, $CaCO_3$–DMF, or Dabco–DMF resulted primarily in conversion (60–75% yield) to an isomeric chloride **22** and smaller amounts (16–18% yield) of alcohol **14a**.



To establish the stereochemistry of the two isomeric chlorides, the NMR spectra were compared with the NMR specta of the pair of alcohols **14a**, which must have an α-oriented hydroxyl group, and its epimer **23**, which was the exclusive $NaBH_4$ reduction product of **19** where α-attack would be expected. The data which are summarized in Table I show that the NMR spectra of **21** and **23** are essentially superimposable except for the shift of H-14, as expected; therefore **21** is the β and **22** is the α isomer. This is also indicated by the half-height widths of the H-12 signals which show that the substituents on C-12 are quasi-axial in **19a** and **22** and quasi-equatorial in **21** and **23**. Consequently, $POCl_3$ or $SOCl_2$ treatment of **14a** has resulted in inversion and $LiCO_3$, $CaCO_3$, and Dabco in DMF treatment of **21** has produced an unusually facile halide inversion. Chlorination of alcohols with thionyl chloride is known to proceed with inversion, but there are few

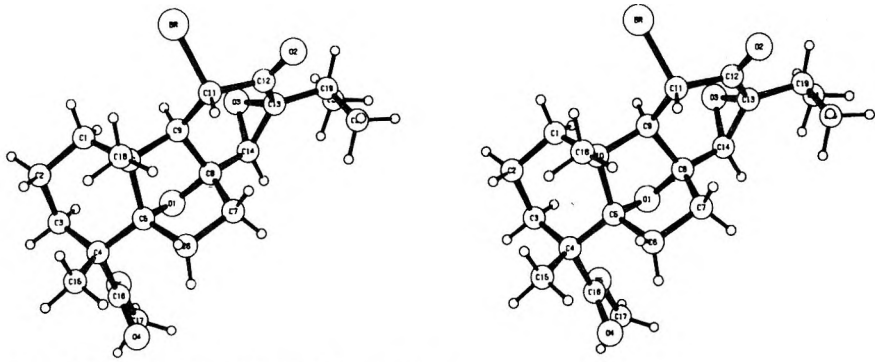


Figure 1. Stereoscopic view of **24**. Atoms are shown as arbitrary spheres.

Table II. Crystal Data for 24

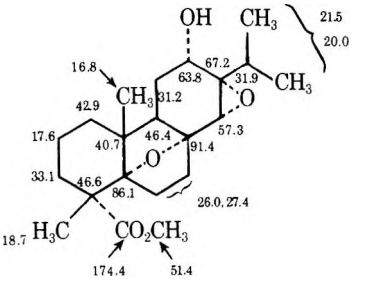
Formula $C_{21}H_{29}BrO_5$
a = 6.106 (2) Å
b = 10.868 (2) Å
c = 31.175 (8) Å
Space group $P2_12_12_1$, Z = 4
d_{calcd} 1.416 g cm^{-1}

precedents for the conversion of alicyclic alcohols to chlorides with $POCl_3$.[18,19] The unusual epimerization **21** → **22** is dealt with in a separate section below.

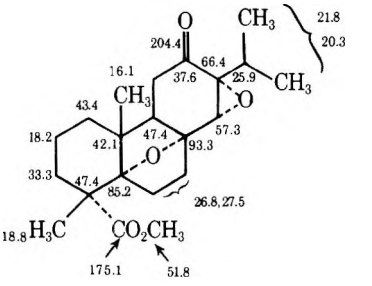
Although efforts to prepare a Δ^{11} derivative had failed, positive evidence for structure **14a** could be adduced in the following manner. Treatment of **19** with pyridinium bromide perbromide afforded a bromo ketone **24** whose NMR spectrum displayed a sharp doublet (J = 12 Hz) at 4.04 ppm for the proton on carbon carrying the bromine atom. This eliminated the alternative structure derived from **13** which should have exhibited a singlet. The large value for $J_{9,11}$ showed that H-9 and H-11 were trans diaxial and that the C-11 bromine atom was equatorial as shown in the formula.

Additional evidence in favor of formula **14a** derives from the ^{13}C NMR spectrum of A, which exhibits the requisite number of quartets (five, one of which is the methoxyl carbon at 51.4 ppm), triplets (six), doublets (four), and singlets (six, one of which is the carbonyl carbon at 174.4 ppm). It contains five other signals below 50 ppm, i.e., three singlets at 91.4, 86.1, and 67.2 ppm and two doublets at 63.8 and 57.3 ppm. The doublets must be assigned to C-12, the hydroxylated carbon, and to C-14 carrying an epoxidic oxygen. A considerable body of information has now accumulated which shows that epoxidic carbons carrying no other heteroatoms rarely, if ever, absorb at frequencies below 75 ppm,[20] whereas α carbons of substituted tetrahydrofurans absorb at considerably lower field.[21] Thus the singlets at 91.4 and 86.1 ppm are quite incompatible with formula **13**, but support formula **14a**. This conclusion is corroborated by the ^{13}C NMR spectra of two 8,9-epoxypimaranes **25** and **26**[22] whose epoxidic carbons resonate at 63.4 and 70.2 ppm (for **25**) and at 64.9 and 71.9 ppm (for **26**).

Assignments of frequencies in the ^{13}C NMR spectrum of **14a** are shown below. Comparison with the data of Wenkert and Buckwalter[23a] for other resin acids permitted identification of most signals except for three triplets (27.4, 26.0, and 31.2 ppm of C-6, C-7, and C-11), two doublets (57.3 and 63.8 ppm of C-12 and C-14), and two singlets (86.1 and 91.4 ppm of C-5 and C-8). Comparison with the ^{13}C NMR spectrum of **19** allowed assignment of the C-11, C-12, and C-14 signals. Two of the unassigned triplets of **14a** remained relatively unchanged, while the third underwent a downfield shift (31.2 → 37.6), hence was assignable to C-11. The remaining two triplets were assigned to C-6 and C-7, a distinction between them being impossible on the basis of shift arguments. Of the two unassigned doublets of **14a**, one underwent a profound downfield shift (63.8 → 204.4), hence was that of C-12. The only other signal of **14a** which was appreciably shifted on oxidation of **14a** to **19** was that of C-15 (31.9 → 25.9). This is not surprising since the models indicate that C-15 is situated in the shielding cone of the carbonyl π system.



14a[a]



19[a]

[a] Assignments at C-5 and C-8 may be interchanged.

Clearly the only structure compatible with the evidence presented so far is **14a**. There remained, however, the question of stereochemistry at C-10. If formation of a radical anion of type C (Scheme I) were the initial step in the pathway leading to intramolecular hydrogen transfer, fragmentation of anion radical C to H and recombination as sketched in Scheme II could conceivably lead to epimerization at C-9 via anion radical I. Anion radical J could not be involved, however, as products resulting from attack on the C-10 methyl group[23b] were not observed. To eliminate the ambiguity at C-9, an x-ray diffraction study of the bromo derivative **24** was undertaken.

X-Ray Analysis of 24. Crystal data for **24** are listed in Table II. Figure 1 is a stereoscopic drawing of the molecule which confirms the proposed structure and shows that C-9 has not undergone epimerization. Tables III, IV, and V containing bond lengths, bond angles, and certain torsion angles are available as supplementary material.

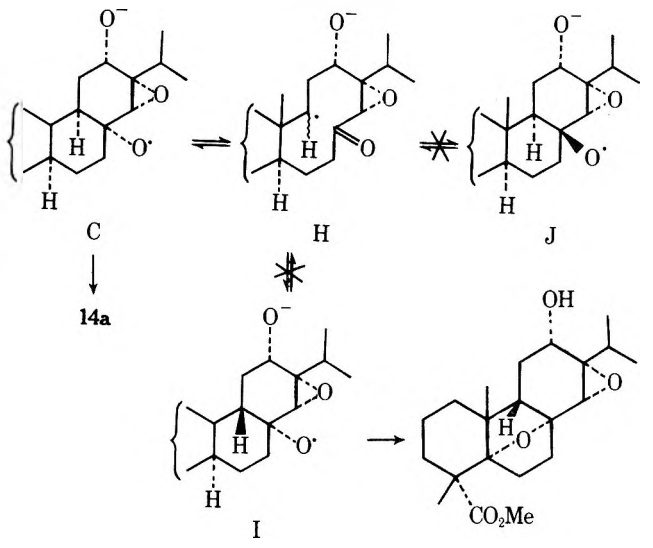
Examination of molecular models of **14a**, **21**, and **22** now suggests a reason for their resistance toward E2 elimination. When the C-12 substituent is α oriented, obstruction of the

Table VI. NMR Spectrum of 27 (270 MHz)[a]

H-6	5.65 dd ($J_{6,7\alpha}$ = 2.8, $J_{6,7\beta}$ = 7.4 Hz)
H-7a	2.36 dd ($J_{7\alpha,7\beta}$ = 16.8 Hz)
H-7b	2.52 dd
H-9	2.03 dd br ($J_{9,11\alpha}$ = 2.7, $J_{9,11\beta}$ = 8.3 Hz)
H-11α	2.31 dd ($J_{11\alpha,11\beta}$ = 15.3 Hz)
H-11β	3.01 dd
H-14	3.36 d ($J_{9,14}$ = 1 Hz)
H-15	2.38 sept (J = 7 Hz)
H-16,[b]H-17[b]	0.90 d, 0.98 d (J = 7 Hz)
H-19[b]	1.34
H-20[b]	0.88
OMe[b]	3.72
OH	3.21 br

[a] In $CDCl_3$. Values in parts per million downfield from internal Me_4Si. Unmarked signals are singlets. [b] Three protons.

Scheme II



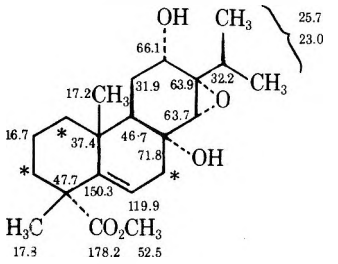
β face by the C-10 methyl group and H-7β effectively blocks attack by base on H-11β. When the C-12 substituent is β oriented as in **21**, the proper orientation for E2 elimination would result in distortion of ring C to a half-chair in which there is severe interaction between H-7β and the C-12 substituent. An attempt to prepare the Δ^{11} olefin by dehydration of **14a** under E1 condition (refluxing acetic acid) which do not require trans-antiparallel geometry resulted only in formation of **14b** (68% yield), presumably because of the difficulty in inducing a positive charge on C-12.

Structure of B. With the structure of A firmly established as **14a**, formula **18a** for B seemed more plausible than ever on mechanistic grounds and was supported by the 270-MHz spectrum of its acetate **18b**. The allylic region clearly showed two sharp doublets of doublets at 2.27 and 2.42 ppm (H-7a and H-7b) which constituted the AB part of an ABX system (J_{AB} = 15.9 Hz), the X part (H-6) being represented by a doublet of doublets at 5.66 ppm in the vinylic region (J_{AX} = 2.7, J_{BX} = 7.4 Hz). The multiplicity of the A and B signals was inconsistent with formulas **16** and **17**, but in conformity with **18**. The remaining low-field signals resembled those of **14b**, a one-proton doublet of doublets at 5.49 ppm (H-12) being coupled to H-11 ($J_{11\alpha,12}$ = 5.2, $J_{11b,12}$ = 10 Hz) and a sharp singlet at 3.04 ppm being identifiable with H-14.

Attempted dehydration of **18a** led to complex mixtures as did its ozonolysis. Oxidation of **18a** with Jones reagent furnished the α-keto epoxide **27** which yielded complex mixtures on treatment with $POCl_3$ or chromous chloride. However, the 270-MHz NMR spectrum of **27** (Table VI) furnished compelling evidence for the structure as postulated.

The protons α to the carbonyl group (H-11α and H-11β) were clearly doublets of doublets as required by formula **27**. Irradiation at the frequency of H-11α collapsed the signal of H-11β to a doublet and established the identity of H-9 as a doublet of doublets at 2.03 ppm which was broadened by "W" coupling to H-14, a phenomenon frequently encountered in this series of compounds (cf. Table I). The signal of the olefinic proton (H-6) at 5.65 and two signals at 2.36 and 2.52 ppm represented a second ABX system of the type QQC=CHCH$_2$Q where Q must represent a quaternary center since A, B, and X were not coupled to other protons and since the magnitude of J_{AB} (16.8 Hz) corresponded to a geminal coupling constant. This information can be accommodated only by **27**; hence **18a** is the structure of the precursor B.

The ^{13}C NMR spectrum of **18a** (see below) is in accord with the postulated structure. Frequencies were assigned by



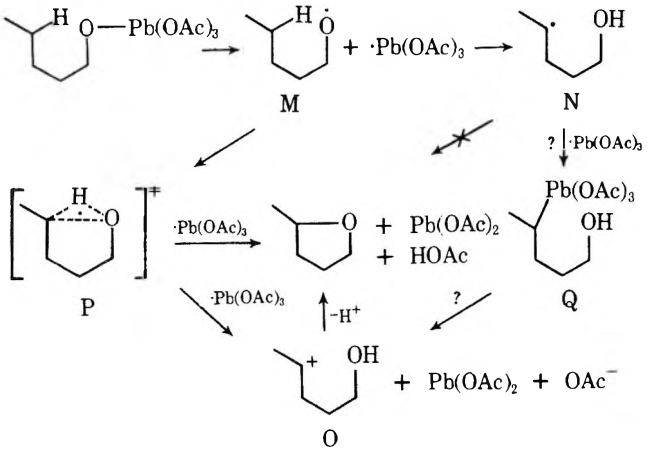
18a (*see Discussion)

comparison with **14a** and **19**. The two downfield doublets at 66.1 and 63.7 ppm were tentatively assigned to C-12 and C-14, respectively, by noting that C-12 is further downfield in **14a** than C-14 (63.8 vs. 57.3 ppm). The possible effect of a hydroxyl instead of an ether oxygen on C-8 was not considered in making this assignment; it is conceivable, but not likely, that the deshielding effect of a C-8 hydroxyl group could reverse the assignments. The singlets at 68.9 and 71.9 ppm were tentatively assigned to C-13 and C-8, respectively, by noting that C-13 occurred at 67.2 and 66.4 ppm in **14a** and **19**. Although the C-3 triplets of **14a** and **19** occurred near 33 ppm, the effect of replacing the 5–8 ether bridge by a 5,6 double bond on C-1 and C-3 was uncertain; no attempt was made therefore to assign the three triplets at 36.5, 33.5, and 32.2 ppm to C-1, C-3, and C-7, specifically.

Discussion

Formation of the unexpected "long range" oxidation products **14a** and **18a** on treatment of **5** with $FeSO_4$ is a new variant of the functionalizations and remote oxidations which proceed through oxy radicals generated through homolysis of an O–X bond, such as the lead tetraacetate oxidation of alcohols,[24] the lead tetraacetate–iodine reaction,[25] the photolysis of nitrites (Barton reaction), the cleavage of hydroperoxides with ferrous sulfate and cupric acetate,[26] and others.[17] A tentative pathway to **14a** and **18a** has already been adumbrated in Scheme I. In the lead tetraacetate oxidation where an oxy radical M formed by homolytic cleavage of a lead alkoxide[24,25] induces 1,5-hydrogen transfer (Scheme III) and which may be taken as a close analogy to the reaction under discussion here, direct displacement of hydrogen on oxygen by the ensuing carbon radical N is considered unfavorable[25] and other pathways which can generate tetrahydrofurans have been suggested. In rigid systems like **5**, where intramolecular hydrogen abstraction is very favorable, ether formation apparently proceeds without intervention of carbonium ions O (equivalent to G of Scheme I) and it is postulated that a three-centered radical species of type P is directly oxidized to tetrahydrofuran. In aliphatic systems, carbonium ions of type O, presumably also formed by oxidation of P, appear to be present and may either cyclyze to tetrahydrofurans or be

Scheme III



deprotonated to olefins. The intermediacy of a species Q which could subsequently decompose to O has not been conclusively established.

Evidence for an oxidation step in the ferrous ion reaction of **5** was obtained by varying the concentration of Fe(II) (Table VII). Reduction of **5** to either of the anion radicals C or D (Scheme I) requires 1 molar equiv of Fe(II) whereas reduction of **5** to **6** requires 2. Table VII shows that reaction of **5** with only 0.5 molar equiv of ferrous ion (entries **6** and **7**) resulted in practically complete conversion to **6**, **14a**, and **18a**. Since at least 1.54 molar equiv of ferrous ion is required for complete conversion to the amounts of **6**, **14a**, and **18a** in entries **6** and **7**, an oxidation step requiring the regeneration of ferrous ion must be involved. Inclusion of an oxidation step in the mechanism is consistent with the previously mentioned view that direct displacement of an oxygen-bound hydrogen by a carbon radical to generate tetrahydrofuran **14a** is unfavorable. Scheme I includes such an oxidation step which for simplicity's sake is listed as proceeding via carbonium ion G.

In the case under discussion, there are three conceivable conformations for radical anion C. Clearly hydrogen abstraction from C-5 cannot occur in the chair-chair-boat conformation R initially formed from **5**, the C–O bond distance being ~4.1 Å and the equatorial C–O bond pointing away from the C–H bond which is to be attacked. In the all-chair arrangement S which is a priori expected to be the most stable conformation, the C–O distance and the geometry for H abstraction are equally unfavorable. However, in the chair-boat-chair conformation T, the C–O distance is 2.6 Å, within the specified limits,[25] and although the transition state for 1,5-hydrogen transfer would not be chairlike,[17] the geometry

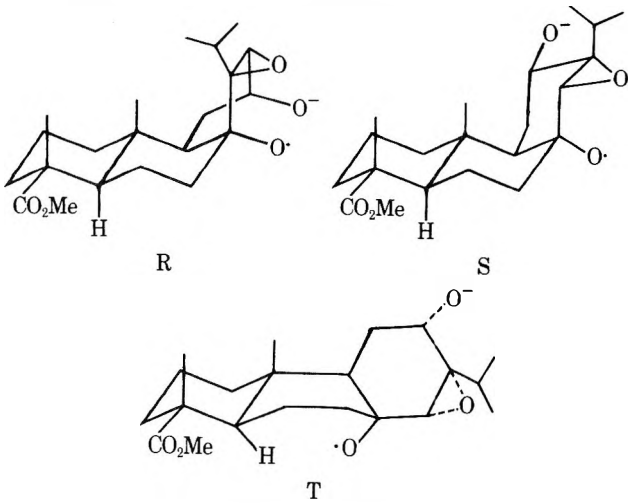


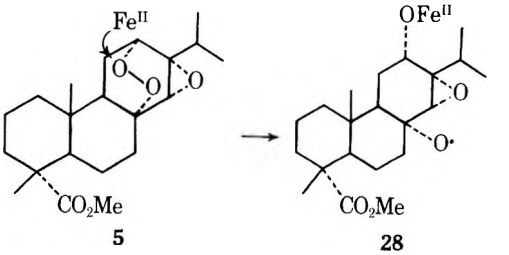
Table VII. Reaction of 5 with Various Concentrations of $FeSO_4$[a]

Entry	[Fe(II)] molar equiv	Yield, % 6	14a	18a	Total recovery
1	10.00	32.5	28.0	33.5	94.0
2	2.00	35.0	33.5	29.0	97.5
3	2.00	34.0	32.0	30.5	96.5
4	1.00	34.0	35.0	27.5	96.5
5	1.00	31.5	32.5	30.0	94.0
6	0.50	28.0	40.0	27.0	95.0
7	0.50	26.0	38.5	26.0	90.5
8	0.25	26.0[b] / 16.5[c]	36.0[b] / 23.0[c]	25.0[b] / 16.0[c]	92.0[d]

[a] See Experimental Section for details. [b] Yields based on amount of **5** which reacted. [c] Overall yields. [d] includes recovered **32** (see Experimental Section).

is suitable for ready collinear attack on H-5 by the oxy radical on C-8.

Two questions concerning the mechanism of reaction of **5** with ferrous ion remain. First, to what extent are the two anion radicals C and D formed, and second, what is the mechanism of oxidation at C-5 by Fe(III) in the radical ensuing from hydrogen transfer in T? Table VII shows that the ratio of long-range oxidation products **6** and **14a** to reduction product **18a** remains essentially constant over a 40-fold range of concentration of $FeSO_4$ (60/33 in entry 1 and 68/27 in entry 6 represent the two extremes, a difference which is probably statistically not very significant because 5–6% of starting material remained unaccounted for in each case). That the percentage of reduction product remains essentially the same even in the presence of very small amounts of Fe(II) can be accounted for by assuming that in the presence of $FeSO_4$, the ratio C/D is approximately 2:1. C undergoes intramolecular hydrogen transfer and eventual oxidation as soon as it is formed whereas D can undergo only reduction to **6** by ferric ion produced in the remote oxidation step. This suggests that the C-12 oxygen atom of **5** is reduced preferentially by Fe(II). The exact mode of O–O bond rupture of peroxides by $FeSO_4$ is not known but could involve nucleophilic attack by Fe(II) on C-12 oxygen, thus resulting in the alkoxide–ferric complex **28** which is



similar to that generally written for the reaction of acyclic peroxides with cuprous ion.[26,27] The preferential formation of one radical anion is consistent with the observation that reaction of ferrous ion with alkyl hydroperoxides principally yields alkoxy radicals and hydroxyl ions.[28] Steric factors, electronic factors, or relative stabilities of the oxy radicals and oxy anions involved could all account for this; in the present case, preferential attack by ferrous ion on the C-12 oxygen for steric reasons to give an alkoxide–ferric complex **28** similar to that written for reaction of acyclic peroxides with cuprous ion[26,27] seems plausible, but is at variance with the preferred attack[13] by triphenylphosphine on the C-8 oxygen of **5**, where the oxygen is removed as triphenylphosphine oxide.

Walling[29] has suggested that ease of reduction of carbon radicals parallels the stability of the carbanion formed and

suggests that this reduction occurs by an outer-sphere electron transfer. The same may hold for the peroxide reduction as well.

Oxidation of radicals by Cu(II) has been extensively studied by Kochi.[30] These oxidations apparently occur by one of two inner-sphere electron transfer processes shown in Scheme IV.

Scheme IV. Oxidation of Carbon Radicals by Cupric Ion

electron-transfer oxidation:

$$\mathrm{R\cdot + Cu^{II}(OAc)_2 \longrightarrow RCu(OAc)_2 \longrightarrow R(-H) + Cu^{I}OAc + HOAc}$$

(29)

$$\mathrm{RCu(OAc)_2 \longrightarrow R^+[Cu^{I}(OAc)_2]^-}$$

ligand-transfer oxidation: X = Hal or pseudo-Hal

$$\mathrm{R\cdot + Cu^{II}X_2 \longrightarrow [R{-}{-}{-}X{-}{-}{-}CuX]^{2-} \longrightarrow RX + Cu^{I}X}$$

or

$$\mathrm{R\cdot + Cu^{II}X_2 \longrightarrow RCuX_2 \longrightarrow [R^+(Cu^{I}X_2)^-] \rightleftharpoons RX + Cu^{I}X}$$

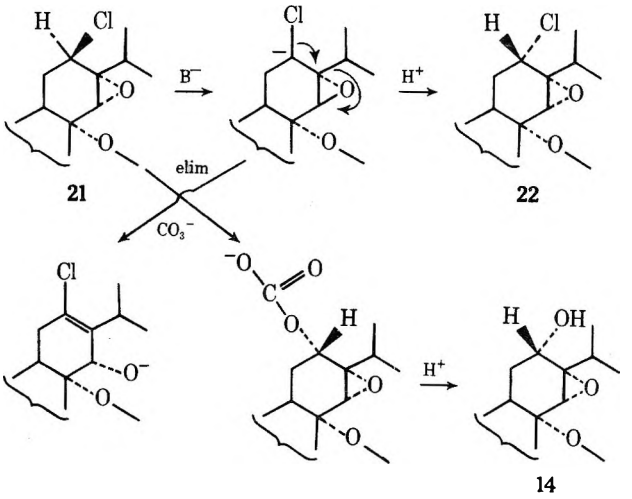
Since Fe(III) is a selective oxidizing agent which oxidizes most easily those radicals which lead to stable carbonium ions, Walling[29] has proposed that oxidation by ferric ion is an outer-sphere electron transfer yielding carbonium ion products. Furthermore, oxidation of substrates which yield highly stable carbonium ions is very fast, oxidation by Cu(II) being appreciably slower than the fastest oxidation by Fe(III). Thus, organoiron species analogous to **29** (Scheme IV) should not be present. The mechanism advanced in Scheme I for oxidation of the C-5 carbon radical proposes such an outer-sphere electron transfer. A transition state similar to P (Scheme III) proposed for oxidation of an alcohol by lead tetraacetate[24,25] is compatible with Scheme I as is the proposed oxidation–cyclization step which could occur by an outer-sphere electron-transfer oxidation by ferric ion in this transition state.

A brief study of the reaction of **5** with other one-electron oxidizing agents was undertaken with interesting results. Substance **5** remained inert toward $MnSO_4$ even on stirring overnight in a nitrogen atmosphere. Reaction with $FeSO_4$–$Cu(OAc)_2$ under the conditions used for intramolecular reactions of acyclic hydroperoxides[31] furnished a very complex mixture (TLC), possibly because the method requires the use of acetic acid as a solvent. In one experiment when the mixture was separated by laborious preparative TLC, 43% of **14a**, but only 7% of **18a**, was isolated although it had been expected that in the presence of $Cu(OAc)_2$, a reagent which usually oxidizes carbon radicals to olefinic products,[30] the major product would have been **18a**. That the solvent acetic acid was not responsible for converting **18a** to **14a** was shown in an independent experiment which resulted in recovery of **18a**.

Reaction of **5** with $VO(AcAc)_2$ in benzene gave the highest yields of long-range oxidation products (58% of **14a** and 28% of **18a**, i.e., 86% total). The remaining material (13%) was an intractable mixture intermediate in polarity between **14a** and **18a**. If **6** were present in this mixture, it must have been formed in very small yield. It appears, therefore, that in the presence of $VO(AcAc)_2$, anion radical C is either formed in much greater proportion than with $FeSO_4$ or that D if formed can equilibrate to C before it is subject to reduction.

The Isomerization 21 → 22. Because of the unusual isomerization of **21** to **22** by the various reagents mentioned previously, the reaction was studied in more detail. $CaCO_3$ in refluxing DMF afforded 57% of **22**, 15% of **14a**, and 5% of recovered **21**. $LiCO_3$ in refluxing DMF gave 70% of **22**, 17% of **14a**, and 11% of unreacted **21**.

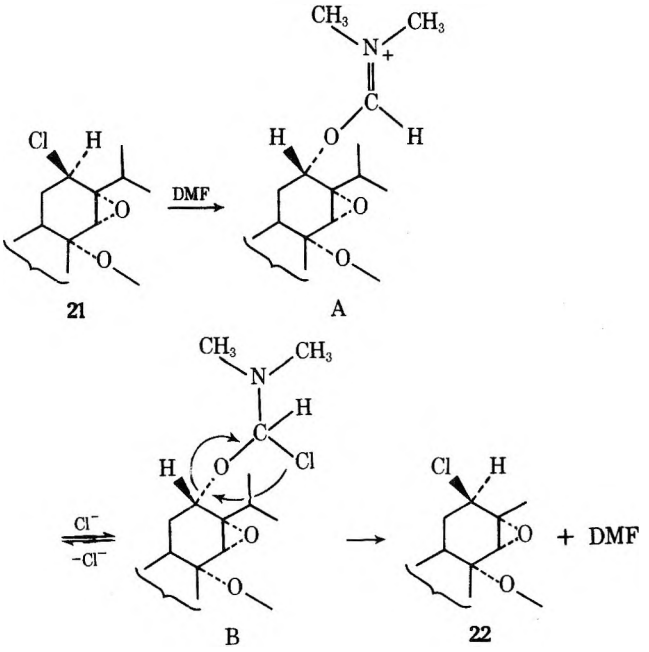
Scheme V



Two mechanisms can be written for this conversion of **21** to **22** and **14a**. The first is a base-catalyzed reaction (Scheme V) in which an anion or partial negative charge is induced α to the electron-withdrawing epoxide group. If this path were operating, the small yield of **14a** must have arisen by nucleophilic displacement of Cl^- by carbonate; on the other hand, the elimination process leading to an olefin of the type shown on the lower left might be expected to predominate.

The second mechanism might involve nucleophilic attack by the DMF oxygen atom on C-13 (Scheme VI) as in the formation of formates from tosylates by heating with DMF.[32] The iminium ion A could now combine with displaced Cl^- to give B which could undergo chlorination at C-12 by an S_Ni mechanism similar to chlorination with thionyl chloride in the absence of pyridine. If this mechanism were in operation, the added base should play no role in the isomerization, i.e., refluxing **21** in DMF alone should produce **22**. In fact, under these conditions, **22** was obtained in 67% yield together with 27% of **14a** and a very small amount of unreacted **21**. While this observation does not completely eliminate the mechanism of Scheme V, it strongly supports that of Scheme VI. The

Scheme VI



reason for the formation of **14a** instead of its formate is not entirely clear, but may be related to the concentration of water in the DMF used for the reaction. The possible implications

of the surprising isomerization of **21** to **22** by DMF will be the subject of further studies.

Experimental Section[33]

Reaction of Sodium Levopimarate with Singlet Oxygen.[14] A solution of 35 g of sodium levopimarate in 400 mL of 95% ethanol was irradiated in the presence of 25 mg of methylene blue with two 150-W incandescent lamps placed near a Hanovia-type reactor and air as the oxygen source, cooling being supplied by a water jacket. After 30 h, the solvent was removed at reduced pressure; the residue was dissolved in water and extracted with ether. The water layer was acidified with 10% acetic acid and thoroughly extracted with ether. The washed and dried ether layers were concentrated at reduced pressure. The residue was dissolved in 50 mL of ethanol and mixed with 25 mL of 2-methyl-2-amino-1-propanol. The precipitate was filtered and recrystallized from ethanol, the filtrates and mother liquors being saved. The precipitate was slurried in ether and mixed with 10% acetic acid to hydrolyze the salt. The ether layer was washed, dried, and evaporated and the gummy residue was recrystallized from methanol–water to give 11.3 g (29%) of **3a**. A second run, identical with the above, gave 14 g (40%) of **3a**.

The ethanolic filtrates from the two preparations of the crude salt of **3a** were combined, hydrolyzed with 5% acetic acid, and extracted with ether. The washed and dried extracts were evaporated and the resulting gum, wt 28.7 g, was placed on 650 g of silica gel column. The following substances were eluted in order: 11 g (17%) of dehydroabietic acid, 1.25 g (1.7%) of **9a**, 8.0 g of a mixture from which 4.2 g (5.8%) of additional **3a** could be obtained by crystallization from methanol–water [the filtrate from this crystallization was evaporated and recrystallized from $CHCl_3$ to afford 3.2 g (5.4%) of impure **8a**], and lastly 1.2 g (1.7%) of **4a**.

Recrystallization of crude **9a** from methanol–water afforded material of mp 152–153 °C, which had NMR signals at 5.84 t (J = 1.5 Hz, H-14), 4.53 m (H-12), 1.22, 1.22 (C-4 and C-10 methyls), 1.09 d and 1.05 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; Found: C, 71.93; H, 9.12.

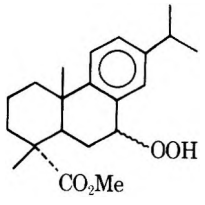
The methyl ester **9b** was prepared with diazomethane and recrystallized from methanol–water and had mp 75–74 °C; IR bands at 1718 and 1246 cm^{-1}; NMR signals at 5.85 t (J = 1.5 Hz, H-14), 4.52 m (H-12), 3.69 (methoxyl), 1.21, 1.21 (C-4 and C-10 methyls), 1.08 d and 1.05 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.88; H, 9.30.

Phenol **8a** had NMR signals (in acetone-d_6) at 6.91 c (H-11, H-12, and H-14), 1.27 (C-4 methyl), and 1.21 (C-10 methyl); mol wt (MS) 274. Methylation with diazomethane and recrystallization from methanol–water afforded **8b**: mp 148–149 °C (lit. 147.5–148.5,[34] 149.5–150 °C[35]); IR bands at 3442 and 1278 (phenol), 1700 and 1254 (ester), 3030, 3018, 1660, 1597, 880 and 835 cm^{-1}. The 270-MHz NMR spectrum exhibited signals at 7.07 d (J = 8.5 Hz, H-11), 6.61 dd (J = 8.5, 2.8 Hz, H-12), 6.49 d (J = 2.8 Hz, H-14), 3.66 (methoxyl), 1.27 (C-4 methyl), and 1.19 ppm (C-10 methyl).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found C, 74.93; H, 8.32; O, 16.82.

Since appreciable amounts of dehydroabietic acid were formed in this reaction, supposedly by air oxidation or disproportionation of levopimaric acid, it seemed reasonable to assume that **8a** had been formed from it by further reaction, either by air oxidation or by reaction with singlet oxygen. Air oxidation of dehydroabietic acid is known to yield **30** as the major product and only minor amounts of **31**,[36] the supposed precursor of **8a**. Thus it would have been surprising



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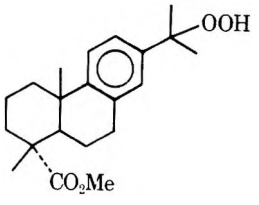

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if **8a** had been formed by this route. The dehydroabietanes **7a**, **7b**, and **7c** were photooxygenated under both acidic and basic conditions, but starting material only was recovered even after several days. Hence **8a** is probably not formed from **7a** by reaction with singlet oxygen. It is also not clear why **8a** is formed from levopimaric acid under the condition of Moore and Lawrence[14] and not under neutral conditions.

Reaction of Levopimaric Acid with Singlet Oxygen. The reaction of 25 g of levopimaric acid with singlet oxygen was carried out as described above (12 h, air as oxygen source). The usual workup furnished 18.4 g (48%) of **3a**. The amine salt filtrates were hydrolyzed to give 10.3 g of gum which was chromatographed over 350 g of silica gel to give 4.7 g (19%) of dehydroabietic acid, 0.8 g (2.7%) of **9a**, and an additional 2.4 g (9%) of **3a**.

Reaction of Methyl Levopimarate with Singlet Oxygen. This is the method of choice for preparation of **3b**. A solution of 10 g of methyl levopimarate in 150 mL of 95% ethanol and 10 mg of methylene blue was irradiated as above (5 h) and concentrated in vacuo. The residue was taken up in ether. The washed and dried ether extract was chromatographed over silica gel to give 7.2 g (65%) of **3b**, 1.4 g (14%) of methyl dehydroabietate, and 0.23 g of **9b**.

Methyl 8β-Hydroxy-12-oxo-13-abieten-18-oate (10). A solution of 50 mg of **9a** in 3 mL of 1 N NaOH in 95% ethanol was refluxed for 10 min, cooled, acidified with 5% acetic acid, and extracted with ether. The washed and dried extract was evaporated and the residue was recrystallized from $CHCl_3$–hexane to give 70 mg of the impure acid. Methylation of 150 mg of this material with diazomethane and recrystallization of the crude product from methanol–water afforded 135 mg (90%) of **10**: mp 107–108 °C; IR bands at 3490, 1723, 1670, and 1250 cm^{-1}; NMR signals at 6.32 d (J = 1.0 Hz), 3.65 (methoxyl), 1.21 (C-4 methyl), 1.08 (C-10 methyl), 0.98 d and 0.97 ppm d (isopropyl methyls).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.27; H, 9.27; O, 18.35.

Methyl 8β-Epoxy-12-abieten-18-oate (11). A solution of 100 mg of **9b** and 80 mg of triphenylphosphine in n-heptane was refluxed for 3 h, cooled, filtered, and evaporated at reduced pressure. The residue was purified by preparative TLC (eluent 1:4 ether–hexane) to give 68 mg of gummy **11**. Further rechromatography gave semicrystalline material which had IR bands at 1722 and 1245 cm^{-1}; NMR signals at 5.55 m (H-12), 3.65(methoxyl), 2.79 d (J = 2.5 Hz, H-14), 1.25 (C-4 methyl), 1.08 d and 0.90 d (J = 6.5 Hz, isopropyl methyls), and 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.49; H, 9.60.

Methyl 8β,14β;12β,13β-Diepoxyabietan-18-oate (12). A solution of 50 mg of $FeSO_4 \cdot 7H_2O$ in 1 mL of water was added to 110 mg of **9b** in 20 mL of 3:2 THF–H_2O with stirring. Reaction was complete after 30 min. The solvent was evaporated, and the residue was diluted with water, acidified, and extracted with ether. The washed and dried ether extract was evaporated; the residue was purified twice by preparative TLC (eluent 3:7 ether–hexane), but could not be induced to crystallize, yield 76 mg (69%); IR bands at 1725 and 1245 cm^{-1}; NMR signals at 3.65 (methoxyl), 3.10 m (H-12), 2.79 br (H-14), 1.24 (C-4 methyl), 1.06 d and 0.95 d (J = 7 Hz, isopropyl methyls), 0.95 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.07; H, 9.69.

Reaction of 5 with Ferrous Sulfate. A. To a solution of 1.0 g of 5[13] in 40 mL of aqueous THF was added with stirring a solution of 0.4 g of $FeSO_4 \cdot 7H_2O$ in 10 mL of water. Brown ferric compounds precipitated immediately. The mixture was stirred at room temperature for 2 h, poured into 300 mL of water, and thoroughly extracted with ether. The washed and dried ether layer was evaporated and the residue separated by preparative TLC (solvent 13:7 ether–hexane).

The least polar material was **14a**, wt 280 mg, mp 129–130 °C. It exhibited IR bands at 3545 (nonbonded hydroxyl), 1712 and 1267 cm^{-1} (ester); NMR signals at 4.03 m (sharpens to multiplet, $W_{1/2}$ = 8 Hz on D_2O exchange, H-12), 3.69 (methoxyl), 3.29 (H-14), 1.30 (C-4 methyl), 1.01 d and 0.89 d (J = 7 Hz, isopropyl methyls), 0.98 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.28; H, 8.79; O. 21.97.

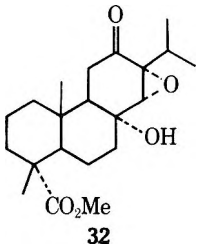
The second band was diol **6**, wt 310 mg, mp 145–146 °C, identical with authentic material.[13]

The most polar substance was **18a**, wt 330 mg, mp 161–163 °C. It had IR bands at 3520, 3458 (nonbonded and bonded hydroxyl), 1740 and 1230 cm^{-1} (ester); NMR signals at 5.76 t (J = 6 Hz, H-7), 4.16 m (sharpens on D_2O addition, H-12), 3.71 (methoxyl), 3.03 (H-14), 2.21 d (J = 6 Hz, 2 p, H-6), 1.40 (C-4 methyl), 1.05 d and 0.94 d (J = 7 Hz, isopropyl methyls), 0.97 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 68.93; H, 8.66; O, 22.19.

B. The reactions described in Table VII were carried out as described above with 200 mg of 5 in 6–10 mL of H_2O, 8 mL of THF, and the appropriate amount of $FeSO_4 \cdot 7H_2O$. The reaction was generally complete immediately after mixing, the solvent was removed at re-

duced pressure, and the residue diluted with water and acidified to facilitate removal of the water-insoluble ferric compounds. The mixture was extracted with ether; the washed and dried ether was evaporated and the residual gum chromatographed by preparative TLC with 13:7 ether–hexane. The three bands were extracted with boiling methanol; the solvent was removed at reduced pressure, the residues were taken up in $CHCl_3$, filtered, and concentrated to give crystalline **6**, **14a**, and **18a**. In one run with 0.25 molar equiv of $FeSO_4$ (entry 8), the product after workup was stirred overnight with silica gel in ether to decompose[37] unreacted **5** to **32**[13] before chromatography.



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Reaction of 5 with $FeSO_4$ and $Cu(OAc)_2$. To 0.220 g of $Cu(OAc)_2 \cdot 2H_2O$ and 0.153 g of $FeSO_4 \cdot 7H_2O$ in 20 mL of glacial acetic acid was added with stirring 0.200 g of **5**. Stirring was continued for 6 h. The usual workup and chromatography revealed at least five products of which 86 mg (43%) was **14a** and 13 mg (7%) was **18a**.

Reaction of 5 with Vanadyl Acetonylacetonate. To a solution of 0.100 g of $VO(AcAc)_2$ in 25 mL of anhydrous benzene was added 0.200 g of **5**. The initially dark green solution turned red and finally dark brown. After 2 h the solvent was removed in vacuo. The residue was chromatographed in the usual fashion to yield 115 mg (59%) of **14a**, 56 mg (28%) of **18a**, and 26 mg of a mixture intermediate in polarity.

Preparation of 14b. A solution of 0.200 mg in 5 mL of pyridine and 2 mL of acetic anhydride was allowed to stand overnight. The mixture was poured into water and extracted with ether. The washed and dried extracts were evaporated and the residue was recrystallized from methanol–ether to give 191 mg (86%) of **14b**: mp 231–232 °C; IR bands at 1729, 1711, 1247, and 1225 cm^{-1}; NMR signals at 5.35 m (H-12), 3.73 (methoxyl), 3.17 (H-14), 2.11 (acetate), 1.30 (C-4 methyl), 0.96 (C-10 methyl), 0.95 d and 0.85 ppm d (J = 6.5 Hz, isopropyl methyls).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.96; H, 8.43; O, 23.61. Found: C, 67.85; H, 8.25; O, 23.82.

When an attempt was made to dehydrate 0.100 g of **5** by refluxing with 25 mL of glacial acetic acid, TLC indicated complete disappearance of starting material after 3 days. Chromatography of the crude product resulted in isolation of 76 mg (68%) of **14b**, presumably because of the difficulty in inducing a positive charge at C-12.

Methyl 5α,8α;13α,14α-Diepoxy-12-oxoabietan-18-oate (19). **A.** A solution of 0.100 g of **14a** in 25 mL of acetone was cooled to 0 °C and treated with Jones reagent dropwise until the orange-brownish color persisted. After 15 min ice was added and the mixture was extracted with ether. The washed and dried extract was evaporated. Recrystallization of the residue from methanol–water gave 94 mg (94%) of **19**: mp 159–162 °C; IR bands at 1710 (double strength) and 1260 cm^{-1}; NMR signals at 3.72 (methoxyl), 3.53 (H-14), 1.31 (C-4 methyl), 1.00 (C-10 methyl), 0.89 d and 0.81 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34; O, 22.07. Found: C, 69.62; H, 8.55; O, 22.01.

B. Oxidation of 50 mg of **23** in the same manner afforded 47 mg (95%) of **19**.

Methyl 5α,8α-Epoxy-12-oxo-13-abieten-18-oate (20). Chromous chloride was prepared by the literature method[38] from 10 g of Zn dust, 5 g of $CrCl_3$, and 2 mL of concentrated HCl; 14 mL of the resulting solution was added to 0.125 g of **19** in 21 mL of glacial acetic acid (CO_2 atmosphere). After 5 min the solution was poured into 150 mL of water and extracted with ether. The washed and dried ether extracts were evaporated; the solid residue was recrystallized from hexane and then from methanol to give 0.115 g (97%) of **20** which had IR bands at 1728, 1668, and 1252 cm^{-1}; NMR signals at 6.87 d (J = 1.0 Hz, H-14), 3.68 (methoxyl), 1.30 (C-4 methyl), 1.30 (C-4 methyl), 1.07 (C-10 methyl), 0.97 d and 0.95 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.84; H, 8.56; O, 18.80.

Methyl 12β-Chloro,5α,8α;13α,14α-diepoxyabietan-18-oate (21). **A.** A solution of 0.200 g of **14a** in 10 mL of pyridine was cooled to 0 °C and stirred overnight with 1 mL of $POCl_3$. The mixture was cautiously diluted with ice and 50 mL of water and then extracted with ether. The washed and dried ether layers were evaporated. The solid residue was recrystallized from methanol–water to give 0.192 g (91%) of **21**, mp 137–138 °C, IR bands at 1710 and 1668 cm^{-1}. Significant peaks of the NMR spectrum are given in Table I. The mass spectrum exhibited the molecular ion at m/e 382 with a large (30%) peak at m/e 384.

Anal. Calcd for $C_{21}H_{31}O_4Cl$: C, 65.87; H, 8.16; Cl, 9.26. Found: C, 66.20; H, 8.16; Cl, 9.14.

B. Reaction of 0.200 g of **14a** with 1 mL of $SOCl_2$ in 10 mL of pyridine followed by the same workup gave 0.170 g (81%) of **21**.

Methyl 12α-Chloro,5α,8α;13α,14α-diepoxyabietan-18-oate (22). **A.** A solution of 0.15 g of **21** and 0.120 g of $CaCO_3$ in 25 mL of DMF was heated at reflux for 18 h. The mixture was poured into 50 mL of water and extracted with ether. The washed and dried ether layers were evaporated at reduced pressure. The residue was purified by preparative TLC (eluent 3:2 ether–hexane). The least polar product (7 mg) was unreacted **21** and the most polar product (21 mg, 15%) was **14a**. The product of intermediate polarity (86 mg, 57%) was **22** which was recrystallized from methanol and methanol–water, mp 178–180 °C, IR bands at 1713 and 1268 cm^{-1}. Significant NMR signals are listed in Table I. The mass spectrum exhibited the molecular ion at m/e 382 and a large (30%) peak at m/e 384.

Anal. Calcd for $C_{21}H_{31}O_4Cl$: C, 65.87; H, 8.16; Cl, 9.26. Found: C, 66.21; H, 8.17; Cl, 8.94.

B. A mixture of 0.175 g of **21**, 0.140 g of Li_2CO_3, and 25 mL of DMF was refluxed for 24 h and worked up in the same way. After chromatography, the yields were 122 mg (70%) of **22**, 21 mg of unreacted **21**, and 28 mg (17%) of **14a**.

C. A soltion of 10 mg of **21** and 100 mg of Dabco in 25 mL of DMF was refluxed for 6 h. TLC showed one major product (**22**, identified by NMR spectrometry) and a minor product, but the mixture was not separated.

D. A solution of 0.100 g in 25 mL of DMF was refluxed for 18 h. Chromatography after the usual workup resulted in isolation of 67 mg (67%) of **22** and 26 mg (27%) of **14a**.

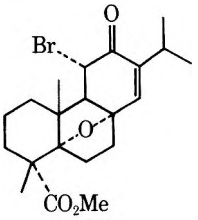
Methyl 5α,8α;13α,14α-Diepoxy-12β-hydroxyabietan-18-oate (23). To 50 mg of $NaBH_4$ in 10 mL of anhydrous methanol was added dropwise with stirring 0.300 g of **19** in 25 mL of methanol. After 1 h, the mixture was decomposed by cautious addition of 10 mL of water, acidified with dilute HCl, and extracted with ether. The washed and dried ether extract was evaporated and the residue was recrystallized from $CHCl_3$–hexane, yield 0.276 g (92%), mp 202–204 °C, IR bands at 3472, 1690, and 1275 cm^{-1}. Significant peaks of the NMR spectrum are listed in Table I.

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 68.98; H, 8.73; O, 21.86.

Methyl 11α-Bromo-5α,8α;13α,14α-diepoxy-12-oxoabietan-18-oate (24). A solution of 0.300 g of **19** and 0.275 g of pyridinium bromide perbromide in 15 mL of glacial acetic acid was heated on a steam bath for 30 min, cooled, diluted with 100 mL of water, and extracted with ether. The washed and dried extract was evaporated. The residual gum was purified by preparative TLC (three elutions with 2:5 ether–hexane). The major band was isolated and rechromatographed to remove yellow impurities. Recrystallization from hexane afforded 0.193 g (58%) of **24**, mp 153–154 °C, IR bands at 1715 (double strength) and 1262 cm^{-1}. The 270-MHz spectrum exhibited signals at 4.08 d (J = 11.5 Hz, H-11), 3.72 (methoxyl), 3.60 (H-14), 2.85 dd (J = 11.5, 2 Hz, H-9), 2.48 sept (J = 7 Hz, H-15), 1.31 (C-4 methyl), 1.19 (C-10 methyl), 0.90 d and 0.86 ppm d (J = 7 Hz, isopropyl methyls). The low-resolution mass spectrum exhibited the molecular ion at m/e 440; a peak of equal intensity at m/e 442 showed the presence of Br. Single crystals for x-ray analysis were prepared by recrystallization from ethyl acetate–hexane.

Anal. Calcd for $C_{21}H_{29}O_5Br$: C, 57.15; H, 6.63; Br, 18.10. Found: C, 57.45; H, 6.58; Br, 18.63.

A minor product, isolated from the first chromatogram and rechromatographed for further purification, was recrystallized from methanol–water, yield 93 mg (27%), mp 163–164 °C. Structure **33** was



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assigned to this substance which exhibited NMR signals at 6.96 d (J = 1 Hz, H-14), 4.50 d (J = 13 Hz, H-11), 3.68 (methoxyl), 1.33 and 1.31 (C-4 and C-10 methyls), 1.01 d and 0.97 ppm d (J = 7 Hz, isopropyl methyls). The low-resolution mass spectrum exhibited the molecular ion at m/e 424 and a peak of equal intensity at m/e 426.

Anal Calcd for $C_{21}H_{29}O_4Br$: Br, 18.79. Found: Br, 18.97.

X-Ray Analysis of Methyl 11α-Bromo-5α,8α;13α,14α-diepoxy-12-oxoabietan-19-oate (19). Single crystals were prepared by recrystallization from ethyl acetate–hexane. Intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystals used for data collection was ca. 0.02 × 0.08 × 0.55 mm. Data were corrected for absorption (μ = 32.3 cm^{-1}). Of the 1661 independent reflections with $\theta < 57°$, 1061 were considered to be observed.

The structure was solved by the heavy atom method and was refined by full matrix least squares. In the final analysis, anisotropic thermal parameters were used for the bromine atom, the oxygens, and all carbon atoms except C(19) and C(21) (see Figure 1 for numbering), and isotropic temperature factors were used for the hydrogen atoms, C(19), and C(21). The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices were R = 0.074 and R = 0.075 for the 1061 observed reflections. Except for two peaks (0.9 and 0.7 e A^{-3}) in the vicinity of the isopropyl group, there were no peaks greater than ±0.4 e A^{-3} on the final difference map. These two peaks indicate some disorder involving the isopropyl group, but no attempt was made to account for it in the calculations. Because of the large estimated standard deviations on the order of 0.02 Å, 1.5°, and 2.5°, respectively (see supplementary Tables III–V), no attempts will be made to discuss individual bond lengths, angles, and torsion angles.

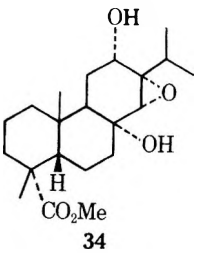
Reactions of 18a. Acetylation. Reaction of 0.150 g of **18a** in 8 mL of pyridine with 2 mL of acetic anhydride in the manner described for **14a** gave a product which could not be induced to crystallize. Purification by preparative TLC (eluent 1:1 ether–hexane) gave 0.136 g (81%) of **18b** which afforded semicrystalline material on being kept in a high vacuum. It had IR bands at 3490, 1722, and 1240 cm^{-1}; NMR signals (270 MHz) at 5.66 dd (J = 2.9, 7.4 Hz, H-6), 5.49 dd (J = 5.2, 10 Hz, H-12), 3.67 (methoxyl), 3.04 (H-14), 2.42 dd (J = 7.4, 15.9 Hz, H-7b), 2.27 dd (J = 2.9, 15.9 Hz, H-7a), 2.10 (acetate), 1.35 (C-4 methyl), 1.06 (C-10 methyl), 1.01 d and 0.87 ppm d (J = 7 Hz, isopropyl methyls). The analytical sample was purified once more by preparative TLC.

Anal. Calcd for $C_{23}H_{34}O_6$: mol wt, 406.2346. Found: mol wt (MS), 406.2346.

Ozonolysis. A solution of 0.150 g of **18a** in $CHCl_3$ was exhaustively ozonized at −78 °C. After warming to room temperature, the ozonide was decomposed by addition of 3 drops of dimethyl sulfide. Analytical TLC of the crude reaction product indicated the presence of several highly polar products; no attempt was made to isolate these substances.

Dehydration. A solution of 0.200 g of **18a** in 15 mL of pyridine was cooled to 0 °C, mixed with 2 mL of $POCl_3$, and allowed to stand overnight at 0 °C. The usual workup gave an intractable mixture which could not be separated satisfactorily by preparative TLC.

Hydrogenation. A solution of 0.200 g of **18a** in 100 mL of ethyl acetate was hydrogenated in the presence of 20 mg of 10% Pd/C at 30 psi of hydrogen for 18 h at which time only partial reduction had occurred. The solution was filtered, reduced with 20 mg of PtO_2 at 30 psi for an additional 4 h, filtered, and evaporated. Recrystallization of the solid residue from $CHCl_3$–hexane gave 146 mg (73%) of a dihydro derivative, mp 215–217 °C, probably **34**. The NMR spectrum



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was not well defined, but the following signals were present: 4.00 (presumably H-14), two methyl singlets at 1.30, 1.08, and two superimposed doublets at 0.93 ppm d (J = 7 Hz). The substance was isomeric with, but not identical with, **6**. Several attempts to repeat this reduction resulted only in recovery of **18a**.

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 21.83. Found: C, 68.72; H, 9.21; O, 21.95.

Methyl 13α,14α-Epoxy-8α-hydroxy-12-oxo-5-abieten-18-oate (27). Oxidation of 0.100 g of **18a** with Jones reagent as described for **14a** followed by preparative TLC (eluent 1:1 ether–hexane) of the crude product and recrystallization from methanol–water afforded **27**, wt 89 mg (89%), mp 102–103 °C, IR bands at 3465, 1726, 1695, and 1246 cm^{-1}. The NMR spectrum is listed in Table VI.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34; O, 22.07. Found: C, 69.67; H, 8.32; O, 22.32.

Acknowledgment. The aid of Mr. R. C. Rosanske in determining ^{13}C NMR spectra is gratefully acknowledged.

Registry No.—**3a,** 15620-98-1; **5,** 25859-65-8; **8a,** 61597-83-9; **8b,** 22465-59-4; **9a,** 18549-42-3; **9b,** 5309-31-9; **10,** 61591-76-0; **11,** 61617-17-2; **12,** 61617-18-3; **14b,** 61618-21-1; **18a,** 61597-77-1; **18b,** 61597-78-2; **19,** 61597-79-3; **20,** 61597-80-6; **24,** 61597-84-0; **27,** 61597-85-1; **33,** 61597-86-2; **34,** 61617-21-8; sodium levopimarate, 61597-87-3; levopimaric acid, 79-54-9; methyl levopimarate, 61597-88-4; $FeSO_4$, 19468-88-3.

Supplementary Material Available. Tables III, IV, and V listing bond distances, bond angles, and torsion angles of compound **24** (3 pages). Ordering information is given on any current masthead page.

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Fe(II)-Induced Decomposition of Epidioxides Derived from α-Phellandrene[1]

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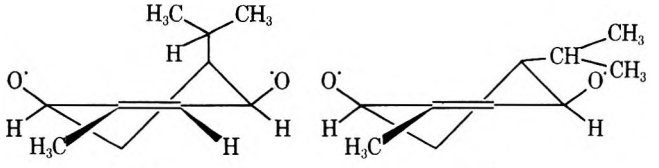
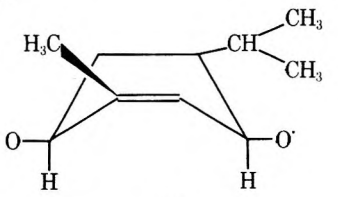
In the Fe(II)-promoted decomposition of the endoperoxides **2, 3, 10, 13,** and **14** prepared from α-phellandrene, the intramolecular 1,5-hydrogen abstraction previously observed in the case of levopimaric acid epidioxide epoxide (**1**) is at best a minor pathway. Structurgs of the various products have been elucidated. A general scheme for the reactions of epidioxides with Fe(II) is presented which involves the Fe(II)–Fe(III) redox system in what superficially appears to be a series of isomerizations and provides a laboratory analogy for the PGG (or PGH) to PGF conversion.

The unexpected formation of remote oxidation products from the reaction of levopimaric acid epidioxide epoxide (**1**) with ferrous ion[2] suggested that other epidioxides might undergo similar reactions if the geometry of the peroxidic oxygen atoms were appropriate for 1,5-hydrogen transfer. Very few of the readily available epidioxides[3] fulfill this condition. In the present communication we report our results in the α-phellandrene series.

Reaction of α-phellandrene with singlet oxygen yields two epidioxides[4,5] which will be referred to as the cis peroxide **2** and the trans peroxide **3**. **3** contains a γ hydrogen (H-8) with suitable geometry and appropriate carbon–oxygen distance for abstraction by the oxygen atom on C-6 if the radical anion formed by reduction of **2**[2] could assume the half-chair conformation **2a**. The methyl hydrogens of the isopropyl side chain are available to C-3 oxygen in both half-chair and both half-boat conformers of **2**. Regardless of the conformation of the radical anion from **3**, there is no hydrogen available to the oxygen atom on C-6. But in two conformers, half-chair **3a** and half-boat **3b**, the methyl hydrogens of the isopropyl radical are accessible to the oxygen on C-3.



2a **3a**

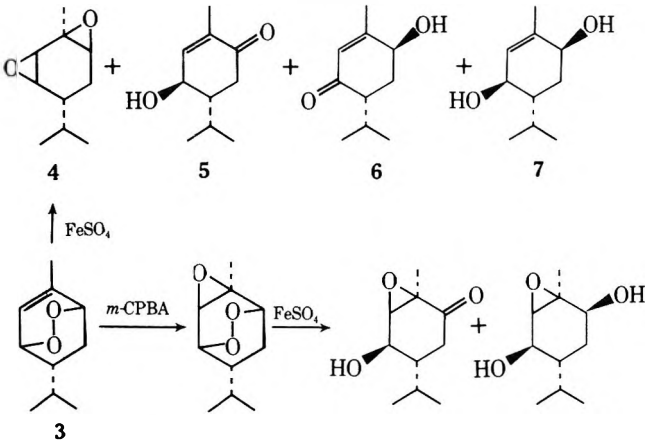


3b

Results

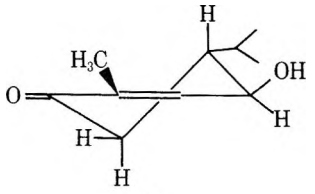
Reaction of trans peroxide **3** with ferrous ion in aqueous tetrahydrofuran gave a mixture of four substances (Scheme I) which were separated by preparative TLC. The least polar

Scheme I



product (26%) was identified as the bisepoxide **4** on the basis of the following evidence. The IR spectrum had no absorption in the carbonyl or hydroxyl region. The NMR spectrum (270 MHz) exhibited a three-proton singlet at 1.51 ppm typical of methyl attached to carbon bearing an oxygen and two methyl doublets of the isopropyl group which showed that long-range oxidation at the site of the methyl groups had not occurred. A one-proton doublet (J = 4 Hz) at 3.12 ppm and two multiplets at 2.87 and 2.91 ppm were appropriate for H-2, H-3, and H-6. Irradiation at 3.12 ppm altered the signal at 2.87 ppm and in the reverse experiment, irradiation at 2.87 ppm collapsed the doublet at 3.12 ppm to a singlet. This allowed assignment of the three peaks at 3.12, 2.87, and 2.91 ppm to H-2, H-3, and H-6, respectively.

The product formed in largest amount (29%) was the γ-hydroxy-α,β-unsaturated ketone **5** (IR bands at 3410 and 1670 cm^{-1}). The NMR spectrum exhibited a broadened doublet (J = 8 Hz) at 4.35 ppm which sharpened on D_2O exchange and was therefore assigned to hydrogen under hydroxyl. The chemical shift of a one-proton multiplet at 6.67 ppm was typical of the β proton of an α,β-unsaturated ketone which was allylically coupled to a vinyl methyl (1.76 ppm) at the α position. The isopropyl methyls were represented by the usual two doublets. A one-proton doublet of doublets at 2.45 ppm (J = 15.9, 3.2 Hz) was assigned to one of the two protons α to the carbonyl group. Irradiation at this frequency altered the pattern of a complex multiplet centered near 2 ppm which therefore represented the second α-keto proton. The large value of $J_{3,4}$ (8 Hz) indicated that **5** is in the half-chair conformation **5a**; this permits assignment of the 2.45-ppm reso-



5a

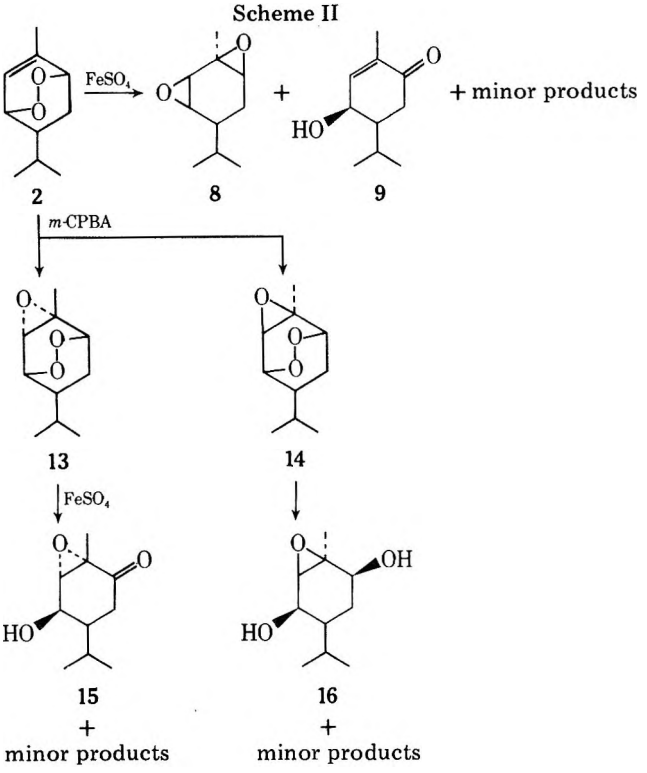
nance to H-5β. In this conformation equatorial H-5β is deshielded by the carbonyl group and the dihedral angle between H-5β and axial H-4 is consistent with the observed coupling constant of 3.2 Hz.

The third product (11%) was the isomeric γ-hydroxy-α,β-unsaturated ketone **6** (IR absorption at 3380 and 1655 cm^{-1}) with significant NMR signals at 5.80 (multiplet of H-Z allylically coupled to vinyl methyl at 2.01 ppm, chemical shift typical of α proton in β-alkyl-α,β-unsaturated ketone) and 4.35 ppm (multiplet of H-6). Two methyl doublets at 0.89 and 0.93 ppm showed that the isopropyl methyls had not been attacked. This substance has recently been reported as a product of the microbiological oxidation of piperitone.[6] The most polar product (18% yield) was the known[7] diol **7**.

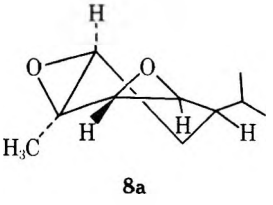
Reaction of the cis peroxide **2** with ferrous sulfate likewise gave a mixture containing two major and two minor fractions (TLC). One of the minor fractions was formed in very small amount only and was not identified. The second minor fraction, while homogeneous on TLC, was a mixture by NMR criteria and could not be separated further. The two major products were isolated in pure form (Scheme II). The IR spectrum of the less polar substance **8** (16%) exhibited no hydroxyl or carbonyl absorptions. In the NMR spectrum (270 MHz) were found the usual two methyl doublets of the isopropyl group, a three-proton resonance at 1.46 ppm characteristic of methyl on carbon carrying single-bonded oxygen, a one-proton doublet of doublets (J = 7, 2.5 Hz) at 2.88 ppm, and an AB system centered at 3.12 ppm (J_{AB} = 5 Hz), the chemical shifts being typical of three protons under epoxidic oxygen. The value of J_{AB} indicated that the two protons in question were vicinal, not geminal; consequently the substance was identified as the diepoxide **8**. The absence of coupling between H-3 and H-4 is presumably due to conformation **8a** in which the H-3, H-4 dihedral angle is close to 90°; this conformation is also in agreement with the values of $J_{5\alpha,6}$ (7 Hz) and $J_{5\beta,6}$ (2 Hz).

The IR spectrum of the product isolated in larger amount (28%, **9**) had hydroxyl and α,β-unsaturated ketone bands. The NMR spectrum exhibited a doublet of quartets (J = 6, 1.5 Hz) at 6.78 ppm and a narrowly split (J = 1.5 Hz) methyl doublet at 1.78 ppm typical of a β-methyl-α,β-unsaturated ketone (cf. the NMR spectrum of **5**), a complex multiplet at 4.42 ppm assigned to hydrogen under hydroxyl, and the AB part of an

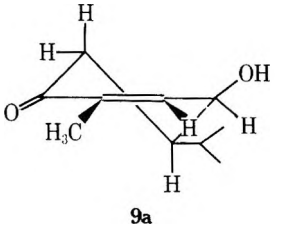
Scheme II



ABX system at 2.56 and 2.44 ppm where J_{AB} = 16.7 Hz (geminal coupling), J_{AX} = 4.3 Hz, and J_{BX} = 12.2 Hz. Clearly this system represented H-5α and H-5β of **9**; the chemical



8a



9a

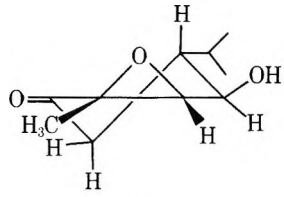
shifts and coupling constants pointed to conformation **9a**, where the larger vicinal coupling is that between H-5β at 2.44 ppm and H-5, equatorial H-5α being at lower field because of the anisotropic effect of the carbonyl group. However, H-5β is deshielded relative to H-5α of **5** because it is under the influence of a pseudoaxial hydroxyl group on C-4.

Reaction of the unsaturated cis aud trans peroxides **2** and **3** with ferrous ion had thus led to the isolation only of "normal" products, i.e., rearrangement and reduction products, and had furnished no substances which might have resulted from long-range oxidation. Therefore, the epoxides of **2** and **3** were prepared to remove the influence of the double bond which permits the formation of diepoxides.

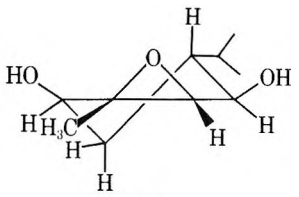
Epoxidation of **3** with *m*-chloroperbenzoic acid gave only one crystalline epoxide which was isolated in 76% yield and was assigned formula **10** since examination of a Dreiding model of **3** showed that the endo isopropyl group hinders attack from the α face. Reaction of **10** with ferrous sulfate furnished only two products (TLC) which were isolated in 36 and 31% yield, respectively.[8]

The less polar material **11** obtained in somewhat larger yield was a hydroxy ketone (IR bands at 3420 and 1700 cm^{-1}). The NMR spectrum exhibited in addition to the two methyl doublets of the isopropyl group and a singlet characteristic of methyl on carbon bonded to oxygen a narrowly split doublet (J = 1.5 Hz) of epoxidic hydrogen at 3.53 and a triplet at 4 ppm which sharpened to a doublet (J = 8.8 Hz) on D_2O exchange. Each half of the doublet was broadened further ($W_{1/2}$

= 4 Hz). A doublet of doublets at 2.46 ppm (J = 16.5, 3.6 Hz) was assigned to one of two protons α to the ketone group, since the larger constant was too large for vicinal coupling, the signals of the remaining two protons being superimposed in a complex multiplet centered at 2.00 ppm. The spectroscopic evidence points to conformation **11a** in which H-3 and H-4 are



11a



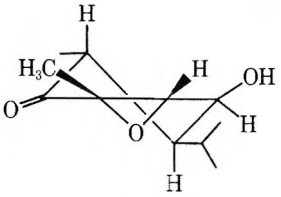
12a

diaxial because of the large value of $J_{3,4}$. Equatorial H-5β at 2.46 ppm is deshielded relative to H-5α; the magnitude of $J_{4,5\beta}$ (3.2 Hz) is consonant with this arrangement (cf. NMR spectrum of **5a**).

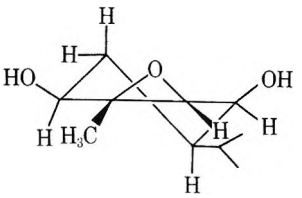
The NMR spectrum of the more polar product, whose IR spectrum indicated the absence of a carbonyl function, exhibited, in addition to the methyls of the isopropyl group and to the methyl on carbon attached to oxygen, signals of an epoxidic proton at 3.34 ppm (J = 2 Hz) and of two protons under hydroxyl on two multiplets at 3.74 and 3.84 ppm which sharpened to a broadened doublet (J = 10, 2–3 Hz) and a more narrowly split apparent triplet on D_2O exchange. Consequently this substance was the reduction product **12.** Molecular models suggested that the half-chair **12a** was the most stable conformation of this diol; the broad doublet at 3.75 ppm could then be assigned to pseudoaxial H-3 and the narrowly split triplet to pseudoequatorial H-6. Other assignments could then be made as follows. A one-proton multiplet at 1.16 ppm (J = 14.5, 12, and 4 Hz) is that of axial H-5α because of the large vicinal coupling constant to H-4 and the much smaller coupling constant to H-6. A doublet of triplets at 1.54 ppm (J = 14.5, ~3 Hz) was that of equatorial H-5β with geminal coupling to H-5α and smaller couplings to axial H-4 and pseudoequatorial H-6. The signal of H-8 was a partially obscured doublet of septets with coupling constants of 7 (to the methyl protons) and ~4 Hz to H-4 which was partially obscured by the methyl singlet at 1.46 ppm.

Epoxidation of **2** afforded two products **13** and **14.**[9] The structure assignment was based on differences in the NMR spectra. The less polar material isolated in 32% yield exhibited the methyl singlet at 1.55 and the H-2 doublet at 3.51 ppm ($J_{2,3}$ = 5 Hz), whereas the more polar product, obtained in 41% yield, displayed the same signals at 1.43 and 3.32 ppm, respectively. The chemical shifts of the more polar product are essentially identical with those of the β-epoxide **10.** Moreover, although in a molecular model of **13** H-2 and the C-1 methyl group are not particularly close to the peroxide bridge, they are certainly much closer than in molecular models of **14.** Consequently the less polar product in which the relevant signals are at somewhat lower field is identified as the α-epoxide **13** and the more polar substance as the β-epoxide **14.**

Reaction of **13** with ferrous sulfate gave a mixture containing one major product; minor substances whose presence was revealed by TLC were not present in sufficient amount to permit adequate characterization. The IR spectrum of the major product isolated in 45% yield exhibited hydroxyl and carbonyl absorption at 3375 and 1698 cm^{-1} and in the NMR spectrum H-2 was a doublet at 3.47 ppm (J = 3.8 Hz). This strongly indicated that the substance was **15** rather than the isomeric 3-keto-6-hydroxymenthane derivative. A multiplet at 4.58 ppm which sharpened to a triplet (J ~ 3 Hz) on D_2O addition could be assigned to the proton under the hydroxyl group. The A and B parts of an ABX system were visible at 2.10 and 2.48 ppm. Since J_{AB} (18.6 Hz) was characteristic of geminal coupling, and J_{AX} and J_{BX} were determined as 11.4 and 6 Hz, respectively, A was the signal of H-5β and B was the signal of H-5α in conformation **15a.** Signals of H-4 and H-8 were complex multiplets centered at 1.59 and 1.74 ppm.



15a



16a

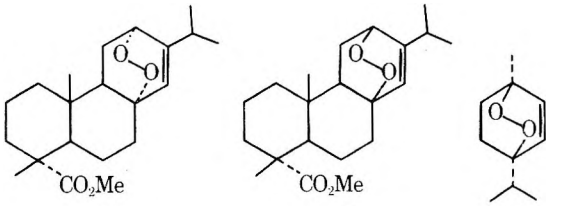
Treatment of **14** with ferrous sulfate in aqueous THF also gave a mixture containing one major and several minor products. The major product could be isolated in 42% yield; its IR spectrum indicated the absence of carbonyl functions and the presence of at least one hydroxyl group. The NMR spectrum retained the doublet of H-2 at 3.38 ppm (J ~ 5 Hz) and exhibited two multiplets at 3.76 and 4.11 ppm which sharpened to a doublet of doublets (J = 11, ~5.5 Hz) and a triplet (J ~ 4 Hz) on D_2O exchange. Consequently we were dealing with epoxy diol **16** whose most stable conformation would be expected to be **16a.** In this conformer the signal at 3.76 ppm would be that of pseudoaxial H-6 which is coupled to axial H-5β (large J) and equatorial H-5α (smaller J) and the signal at 4.11 ppm that of pseudoequatorial H-3 with two smaller coupling constants to H-2 and H-4.

Discussion

Long-range oxidation products were not isolated from the reactions of either the unsaturated peroxides **2** and **3** or the saturated peroxides **10, 13,** and **14** with ferrous sulfate. They were not formed at all from **3** and **10** and if formed from the others, they escaped isolation. Although **2, 13,** and **14** yielded mixtures which might well have included some materials resulting from intramolecular hydrogen transfer, the unidentified fractions which must include substantial amounts of reduction and/or rearrangement products represented rather small proportions of the total product (in no case more than about 20% by TLC).

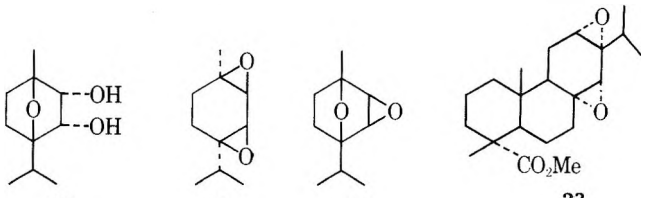
Failure of **2, 13,** and **14,** peroxides in which a priori hydrogen transfer from C-8 to the oxygen atom on C-6 seemed possible, to undergo preferential intramolecular hydrogen abstraction may be due to the circumstance that such hydrogen transfers require transition states analogous to **2a** in which the isopropyl group is axial. On the other hand, it should also be pointed out that the alternative intramolecular hydrogen abstraction process and the only one possible in **3** and **10,** i.e., hydrogen transfer from one of the methyl groups to C-3 oxygen, could easily have escaped detection for the following reason. Reduction by Fe(II) of the primary radical resulting from such a transfer is likely to be faster than oxidation by Fe(III)[10] and the products of such reduction would be the same as the products formed by reduction of the oxygen radical by Fe(II). On the whole, then, it appears in retrospect that the α-phellandrene peroxides were not particularly good candidates for the reaction we wished to observe and our results do not provide a satisfactory answer to the question whether Fe(II)-promoted decomposition of epidioxides can induce long-range oxidation reactions in relatively flexible molecules.

Diepoxides have now been observed as products in all reactions of unsaturated endoperoxides with ferrous ion which have so far been examined (i.e., **2, 3, 17,**[11,12] and **18**[2]) except in the case of ascaridole (**19**). The structure of ascaridole glycol, the major product of the reaction of **19** with $FeSO_4$,[13]



17 18 19

appears to have been reasonably well established as **20** by Jacob and Ourisson,[14] who used the then controversial,[1] but now well-established,[15,16] formula **21** (rather than **22**) for

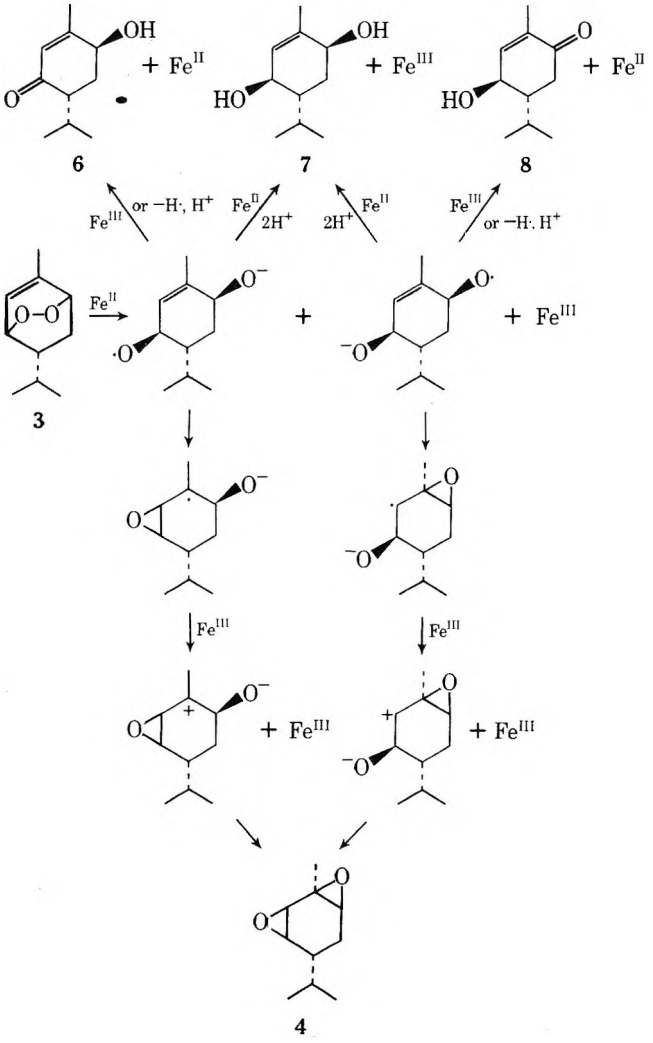


20 21 22 23

isoascaridole (ascaridole glycol anhydride), a substance which is the thermal rearrangement product of **19** and from which ascaridole glycol is also accessible by hydration.[17,18]

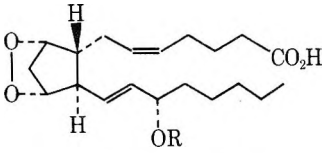
Because of the controversy surrounding the structure of isoascaridole, ascaridole glycol was prepared from ascaridole and ferrous sulfate and its NMR spectrum was recorded at 270 MHz. Two doublets of doublets at 3.79 and 3.56 ppm (J = 5, 9 Hz) which sharpened to an AB pattern at 3.77 and 3.57 ppm (J_{AB} = 9 Hz) with fine coupling (J = 1 Hz) on D_2O exchange

Scheme III

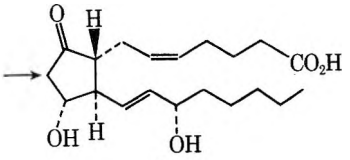


were assigned to two hydrogens under two vicinal hydroxyl groups. The large coupling indicates that the hydrogens are cis (dihedral angle ~0°). The small coupling must be due to "W" coupling between H-2 and H-6, on the one hand, and H-3 and H-5 on the other. The relatively large chemical shift difference (0.2 ppm) between the H-2 and H-3 signals is somewhat surprising, but nevertheless, the NMR spectrum is consistent with formula **20.** Since glycol **20** can also be prepared by hydrolysis of diepoxide **21,** the ferrous ion reaction of ascaridole **19** must proceed through the intermediate nonisolable diepoxide **21.**

As regards the mechanism of formation of the substances described in this report, diols **7, 12,** and **16** are obviously produced by reduction of epidioxides **3, 10,** and **14** with 2 equiv of Fe(II). On the other hand, the formation of **23** from **17** proceeds in 90% yield when only 0.376 molar equiv of $FeSO_4$ is employed.[12] Therefore, just as in the remote oxidations discussed earlier,[2] the mechanism of the epidioxide–diepoxide rearrangement requires a step in which Fe(III) serves as an oxidant. This step is included in Scheme III, which presents a mechanism for diepoxide formation as well as a unified picture for the reactions of unsaturated epidioxides with Fe(II).[19] The trans peroxide **3** which best typifies the diverse pathways open to these substances is used as an example, although not all pathways may not operate in each instance.[21] Of particular interest is the conclusion that just like the isomerization **3** → **4**, the Fe(II)-induced isomerizations **3** → **6** or **3** → **8** involve the Fe(II)–Fe(III) redox system. Thus the Fe(II)-induced rearrangement of epidioxides to ketols may serve as a model for the transformation of prostaglandin G or H to prostaglandin E in vivo under the influence of Fe(II)-based enzyme systems.



PGG_2, R = OH
PGH_2, R = H



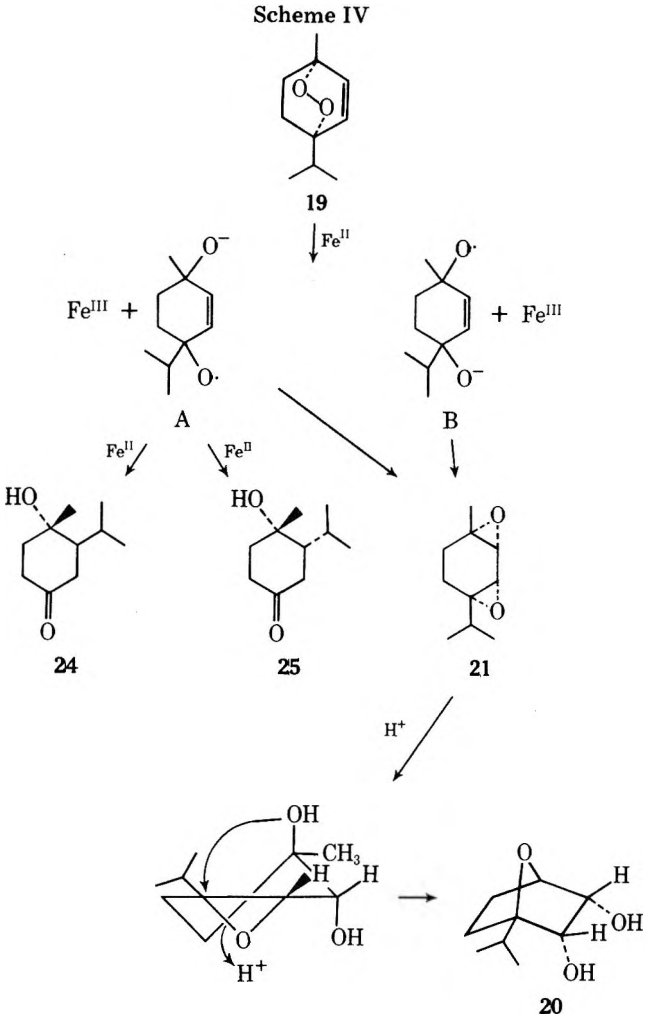
PGE

On the basis of this scheme, a mechanism can also be written for the reaction of ascaridole (**19**) with ferrous ion (Scheme IV) which takes into account that the 1,2-epoxide of isoascaridole (**21**) is more reactive than the 3,4-epoxide[15] and incorporates the observations of Brown et al.[18] that the reaction of ascaridole with $FeSO_4$ is accompanied by formation of **24** and **25.** These substances are presumably formed by expulsion of an isopropyl radical from anion radical A and recombination in Michael fashion at the β position of an α,β-unsaturated ketone.[21a]

Experimental Section

Preparation of 2 and 3. These substances were prepared from commercial α-phellandrene by the literature method.[4,5] The crude reaction mixture was difficult to separate because of the presence of a small amount of ascaridole presumably formed from α-terpinene, which is an impurity in commercial α-phellandrene that cannot be separated by distillation. The crude product was chromatographed over silica gel, a procedure which resulted in the separation of p-cymene from the peroxidic product. The fraction containing **2** and **3** and some ascaridole was separated into its constituents by high-pressure liquid chromatography on a 12-ft Porasil column using 8% ether–hexane as eluent. The cis peroxide **2,** which was a liquid at room temperature but crystallized in the refrigerator, displayed NMR signals (270 MHz) at 6.31 dq (H-2, $J_{2,3}$ = 7, $J_{2,7}$ = 2 Hz), 4.52 dbr

Scheme IV



(H-2), 4.32 m (H-6), 1.90 d (C-1 methyl), 0.96 and 0.98 ppm d ($J \sim 6.5$ Hz, isopropyl methyls). The trans peroxide **3**, mp 37–40 °C, had NMR signals (270 MHz) at 6.17 m (H-2, $W_{1/2} = 12$ Hz), 4.58 m (H-3), 4.42 m (H-6), 1.91 d ($J_{2,7} = 2$ Hz, C-6 methyl), and 0.87 ppm dbr (isopropyl methyls).

Reaction of 3 with $FeSO_4$. A solution of 0.910 g of $FeSO_4 \cdot 7H_2O$ in 15 mL of water was added in one portion to 0.500 g of **3** in 20 mL of THF. A moderately exothermic reaction ensued. The mixture was stirred for 1 h, diluted with 100 mL of water, and thoroughly extracted with $CHCl_3$. The washed and dried extract was evaporated at reduced pressure, and the residue was taken up in a small volume of $CHCl_3$ and filtered to remove 31 mg of crystalline **7**. The filtrate was subjected to preparative TLC (eluent 3:2 ether–hexane). This resulted in four fractions which were isolated and characterized.

The gummy, least polar material was **4** (124 mg, 26%) whose NMR spectrum (270 MHz) had signals at 3.12 d ($J_{2,3} = 4$ Hz, H-2), 2.91 m (H-6), 2.87 m (H-3), 1.51 (C-1 methyl), 0.99 d and 0.94 ppm d ($J = 6.5$ Hz, isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.90; H, 9.67.

The second gummy fraction was **5** which had IR absorption at 3410 and 1670 cm^{-1}; NMR signals (270 MHz) at 6.67 m (H-2), 4.35 dbr ($J = 8$ Hz, simplified on addition of D_2O, H-3), 2.45 dd ($J = 3.2$, 15.9 Hz, H-5β), 1.76 d ($J_{2,7} = 2$ Hz, C-1 methyl), 0.95 d and 0.88 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: mol wt, 168.1149. Found: mol wt (MS), 168.1158.

The third gummy fraction was **6**[6] (55 mg, 11%) which had IR absotion at 3380 and 1655 cm^{-1}; NMR signals at 5.80 m (H-2), 4.35 m (H-6), 2.03 d $J_{2,7} = 1.5$ Hz, C-1 methyl), 0.93 d and 0.89 ppm d (isopropyl methyls).

The most polar fraction was crystalline **7**[7] (62 mg, total yield 93 mg, 18%), mp 164–166 °C. The NMR spectrum tallied with that reported in ref 7.

Reaction of 2 with $FeSO_4$. Reaction of 0.400 g of **2** with 0.828 g of $FeSO_4 \cdot 7H_2O$ in the manner described above required only 15 min for completion. After the usual workup, the crude, gummy product was subjected to preparative TLC (first development with 1:1 ether–hexane, second development with 13:7 ether–hexane). The least polar fraction, wt 41 mg, was still somewhat impure and was not further investigated. The two most polar fractions **4** and **5**, wt 50 and 58 mg, were mixtures by NMR criteria and were also discarded. Fraction **2**, wt 64 mg (16%), was a gum (8) and had NMR signals (270 MHz) at 3.14 d and 3.10 d (AB system of H-2 and H-3, $J_{AB} = 4.5$ Hz), 2.88 dd (H-6, $J = 7$, 2.5 Hz), 1.47 (C-1 methyl), and 0.97 ppm d (superimposed isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: mol wt, 168.1149. Found: mol wt (MS), 168.1186.

Fraction 3, wt 112 mg (28%), was also a gum (**9**) which crystallized on drying and then melted at 40–42 °C. It had IR bands at 3400 and 1660 cm^{-1}; NMR signals (270 MHz) at 6.78 dg ($J_{2,7} = 1.5$, $J_{2,3} = 6$ Hz, H-6), 4.42 m (H-3), 2.56 dd ($J = 16.7$, 4.3 Hz, H-5α) 2.44 dd ($J = 16.7$, 12.2 Hz, H-5β), 1.78 br (C-1 methyl), 1.02 d and 0.95 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.55.

Epoxidation of 2. A solution of 0.500 g of **2** and 0.700 g of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ was stirred for 2 days, washed with dilute KI, sodium thiosulfate, saturated $NaHCO_3$, and water, dried, and evaporated. The residue was *rapidly* chromatographed by preparative TLC (eluent ether–hexane, 1:3) approximately two-thirds up the plate. The less polar product **13** was recrystallized from pentane and had mp 86–88°C; wt 133 mg (32%); NMR signals at 4.26 m, 4.14 m (H-3 and H-6), 3.51 d ($J = 5$ Hz, H-2), 1.55 (C-1 methyl), 0.95 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.69.

The more polar product **14** was recrystallized from $CHCl_3$: mp 83–85 °C; wt 224 mg (41%); NMR signals at 4.42 m and 4.13 m (H-3 and H-6), 3.32 d ($J = 3.5$ Hz, H-2), 1.43 (C-1 methyl), 1.07 d and 1.00 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 8.67.

Epoxidation of 3. A solution of 0.500 g of **3** and 1 g of *m*-chloroperbenzoic acid in 50 mL of $CHCl_3$ was stirred for 2 days and worked up as described in the previous paragraph. The crude product which exhibited only one spot on TLC was recrystallized from $CHCl_3$–pentane to give 0.356 (65%) of **10**. The melting point of this substance was not determined for fear of explosion but was over 110 °C. The NMR spectrum had signals at 4.40 dd ($J = 3$, 6 Hz) and 4.18 m ($W_{1/2} = 10$ Hz, H-3 and H-6), 3.33 dd ($J = 1$, 3 Hz, H-2), 1.43 (C-1 methyl), and 0.98 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.56.

Reaction of 10 with $FeSO_4$. Reaction of 0.370 g of **10** with 0.600 g of $FeSO_4 \cdot 7H_2O$ followed by the usual workup gave a crude product which showed only two spots on TLC. Preparative TLC (17:3 ether–hexane) gave 96 mg (26%) of the less polar product **11** and 78 mg (21%) of the more polar product **12**. In a second run, when THF was removed at reduced pressure before workup, 0.300 g of **3** yielded 0.109 g of **11** (36%) and 92 mg of **12** (31%).

Recrystallization from $CHCl_3$–pentane furnished **11**: mp 76–78 °C; IR bands at 3420 and 1670 cm^{-1}; NMR signals (270 MHz) at 4.00 d (after D_2O exchange, $J = 8.8$ Hz, H-3), 3.53 d ($J = 1.5$ Hz, H-2), 2.46 dd ($J = 16.6$, 3.6 Hz, H-5β), 1.43 (C-1 methyl), 0.93 d and 0.84 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.87; H, 8.67.

Recrystallization from $CHCl_3$–pentane gave **12**, mp 115–117 °C, which had an IR band at 3290 cm^{-1} and NMR signals (270 MHz) at 3.88 t (after D_2O exchange, $J = 4$ Hz, H-6), 3.74 dbr (after D_2O exchange, $J = 10$ Hz), 3.34 d ($J = 2$ Hz, H-2), 2.05 d sept ($J = 4$, 7 Hz, H-8), 1.54 dt ($J = 14.5$, 2.5 Hz, H-5β), 1.48 (C-1 methyl), 1.16 ddd ($J = 14.5$, 4, 12 Hz, H-5β), 0.93 d and 0.80 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.45; H, 9.89.

Reaction of 13 with $FeSO_4$. Reaction of 0.300 g of **13** with 0.500 g of $FeSO_4 \cdot 7H_2O$, removal of THF at reduced pressure, and workup in the usual fashion gave a gum. TLC showed 5–6 spots but only one product was formed in appreciable amount. Preparative TLC (3:2 ether–hexane) and recrystallization of this substance from $CHCl_3$–pentane gave **15**: mp 102–103 °C; wt 134 mg (45%); IR absorption at 3375 and 1698 cm^{-1}; NMR signals (270 MHz) at 4.58 t (after D_2O exchange, $J = 3$ Hz, H-3), 3.47 d ($J = 3.8$ Hz, H-2), 2.48 dd ($J = 6$, 18.6 Hz, H-5α), 2.10 dd ($J = 11.4$, 18.6 Hz, H-5β), 1.74 m and 1.59 m (H-4 and H-8), 1.45 (C-1 methyl), 1.00 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.83; H, 9.12.

Reaction of 14 with $FeSO_4$. Reaction of 0.300 g of **14** with 0.500 g of $FeSO_4 \cdot 7H_2O$ for 1 h, followed by removal of THF and the usual workup, gave a gum. TLC showed several spots but only one product was formed in substantial amount. Preparative TLC (17:3 ether–hexane) resulted in isolation of this substance **16** in semicrystalline form, wt 125 mg (42%). Its IR spectrum showed strong hydroxyl absorption at 3380 cm^{-1}; the NMR spectrum (270 MHz) after D_2O exchange had signals at 4.11 t (J = 4 Hz, H-3), 3.76 dd (J = 5.5, 11 Hz, H-6), 3.38 d (J = 5 Hz, H-2), 1.47 (C-1 methyl), 0.99 d and 0.92 ppm d (isopropyl methyls).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.40; H, 9.74. Found: C, 64.45; H, 9.89.

Registry No.—**2**, 61616-15-7; **3**, 61616-16-8; **4**, 61570-80-7; **5**, 61570-81-8; **6**, 55955-53-8; **7**, 61664-34-4; **8**, 61616-17-9; **9**, 61570-82-9; **10**, 61570-83-0; **11**, 61570-84-1; **12**, 61570-85-2; **13**, 61617-12-7; **14**, 61616-18-0; **15**, 61616-19-1; **16**, 61616-20-4; α-phellandrene, 99-83-2; $FeSO_4$, 19468-88-3.

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(1) Supported in part by a grant from the National Science Foundation (GP-12582).
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(19) The reaction should not be confused with the now well-known thermal rearrangement of epidioxides to diepoxides. The thermal reaction requires higher temperatures and is carried out in a nonpolar solvent. Similarly, the base-catalyzed rearrangement[20] of epidioxides to γ-hydroxy-α,β-unsaturated ketones, etc., differs fundamentally from the transformations described in this report.
(20) N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951).
(21) When the double bond is absent and the epidioxide bridge is attached to at least one tertiary center, stabilization of the initial oxidation products may occur by intramolecular hydrogen transfer followed by oxidation at the remote site as in the case of **1**,[2] or by loss of an alkyl radical which undergoes subsequent oxidation as in the case of dihydroascaridole epidioxide.[18] Therefore an alternative to the direct oxidation of the anion radicals by Fe(II) to give **5** and **6** may be loss at a hydrogen atom which is subsequently oxidized by Fe(III).[21a] (a) **Note Added in Proof.** The possible implications of the Fe(II)-induced decomposition of such epidioxides for prostacyclin and thromborane biosynthesis are discussed in a separate report: J. A. Turner and W. Herz, *Experientia*, in press.
(22) Experimental details have been specified in ref 2.

Fe(II)-Induced Decomposition of Unsaturated Cyclic Peroxides Derived from Butadienes. A Simple Procedure for Synthesis of 3-Alkylfurans

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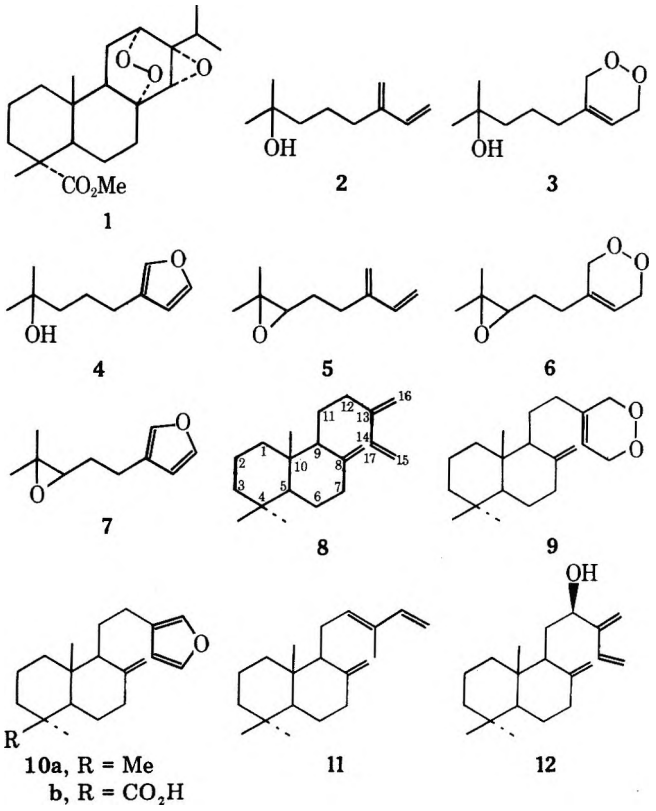
3,6-Dihydro-1,2-dioxins, prepared by reaction of 2-substituted 1,3-butadienes with singlet oxygen, furnish 3-alkylfurans in high yield when treated with ferrous sulfate. The mechanism and limitations of the reaction are discussed. The overall sequence, particularly the last step which involves a redox reaction under extremely mild conditions, may be a model for the biogenesis of naturally occurring 3-alkylfurans.

Fe(II)-induced decomposition of the epidioxide **1** resulted in the unexpected formation of remote oxidation products as the result of intramolecular hydrogen abstraction by the initially formed anion radical.[2] In an attempt to extend this reaction to other substrates with geometries suitable for 1,5-hydrogen transfer[3] we have studied the reaction of Fe(II) with several epidioxides derived from terpenoids which incorporate a 2-alkyl-1,3-butadiene residue. While the original objectives were not realized we have discovered a simple method for making 3-substituted furans which is synthetically useful and may mimic the path by which such substances are formed in nature.

The formation of epidioxides by reaction of homo- and semiannular 1,3-dienes with singlet oxygen is well known,[4] but the preparation of unsaturated cyclic peroxides (3,6-dihydro-1,2-dioxins) from acyclic 1,3-dienes is a relatively new development.[5-7] Very recently, Matsumoto and Kondo[8] examined the reaction of singlet oxygen with a number of acyclic monoterpenoid 1,3-dienes and suggested the following order of reactivity of olefins toward singlet oxygen: trisubstituted monoolefin > 1,3-diene with alkyl substituent at the 2 position > 1,1-disubstituted olefins. Since singlet oxygen is an electrophilic reagent and since mono- and disubstituted olefins react very sluggishly with singlet oxygen,[4] the order of reactivity of olefins toward singlet oxygen suggested by Matsumoto and Kondo[8] can probably be extended as follows: tetrasubstituted monoolefins > trisubstituted monoolefins > 1,3-diene ≫ disubstituted monoolefin and monosubstituted olefin.

Results

As initial substrates for the reaction with ferrous ion we selected the dioxides **3** and **6** from β-myrcene (**2**) and the epoxide **5**.[8,9] Treatment of **3** with ferrous sulfate in aqueous tetrahydrofuran surprisingly furnished only one product (TLC analysis) which was isolated in 81% yield. The IR spectrum displayed hydroxyl absorption as well as bands at 1500 and 880 cm^{-1} characteristic of furans. The 270-MHz



NMR spectrum displayed the typical ABX pattern of a 3-substituted furan (one-proton multiplet of β proton at 6.2 ppm, one-proton multiplet at 7.13 ppm, and one-proton multiplet at 7.25 ppm, J = 1.8 Hz, of the α protons), a two-proton triplet at 2.41 ppm (J = 7 Hz) of the furfurylic protons, and a six-proton siglet at 1.18 ppm. The downfield signals were in good agreement with those reported for 3-hydroxy-2-methyl-5-(3-furyl)-1-pentene;[10] hence the product must be **4**.

Dioxide **6** reacted with ferrous ion in analogous fashion to furnish the furan **7** whose NMR spectrum exhibited the furan resonance at 7.36 (t), 7.26 (m), and 6.29 ppm (m) and the methyl signals at 1.23 and 1.30 ppm. The epoxidic proton signal occurred as a triplet (J = 6 Hz) at 2.77 ppm; two-proton triplets at 2.63 and 1.85 ppm were assigned to H-5 and H-4, respectively.

Two additional substances were examined to determine whether furan formation was a general consequence of the reaction of 3,6-dihydro-1,2-dioxins with Fe(II). These were the naturally occurring labdatrienes sclarene (**8**) and *trans*-biformene (**11**) which can also be prepared, together with *cis*-biformene, from manool.[11]

Reaction of **8** with singlet oxygen gave a relatively poor yield (29%) of peroxide **9**, presumably due to the facility with which the diene polymerizes in air.[11,12] The spectroscopic properties of **9** (see Experimental Section) were in accord with the proposed formulation. Treatment of **9** with ferrous sulfate gave in essentially quantitative yield furan **10a** whose NMR spectrum exhibited the H-17 resonances as broadened singlet at 4.55 and 4.84 ppm and the usual three furan signals, as well as three methyl singlets at 0.79 and 0.68 ppm. The downfield portion of the spectrum was very similar to that of lambertianic acid (**10b**).[13,14]

According to the order of reactivity of olefins toward singlet oxygen presented earlier, one of the conjugated double bonds of **11** would be expected to undergo preferential "ene" reaction. Indeed, the reaction of **11** with singlet oxygen was complete after only 2.5 h and, after reduction of the hydroperoxide with triethyl phosphite, the triene alcohol **12** was obtained in 43% yield.[16] The NMR spectrum exhibited three methyl singlets, a doublet of doublets at 6.34 ppm (J = 18 Hz) assigned to H-14, multiplets at 4.50 and 4.83 ppm (H-17), and a multiplet at 4.34 ppm (H-12). A partially obscured broadened doublet at 5.37 ppm (J = 8 Hz) was identifiable with the resonance of H-15a trans to H-14, whereas a somewhat broadened signal at 4.94 ppm was one-half of a doublet centered at 5.08 ppm (H-15b cis to H-14), the other half being completely hidden. Two narrowly split doublets (J = 1 Hz) at 5.18 and 5.10 ppm were due to the resonance of H-16. These assignments are in good agreement with the NMR spectrum of sclarene (see Experimental Section). Evidence for the configuration of the hydroxyl group depicted in the formula will be presented subsequently.

Table I. Downfield Portion of NMR Spectra of 14a–c

	14a[a]	14b[b]	14c[b]
H-17a	4.47	4.48	4.72
H-17b	4.85	4.86	4.88
H-16, H-15	7.32 d (1.6)	7.3 m	7.3 m
H-14	6.36 t (1.6)	6.37 m	6.37 m
H-12	4.69 dd (9, 3)	4.71 m	4.78 m

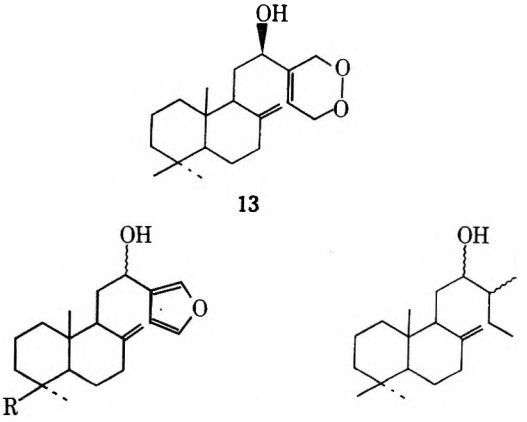
[a] At 270 MHz in $CDCl_3$. [b] At 60 MHz in $CDCl_3$, quoted from ref 17.

Table II. H-17 Resonances of Selected 12-Hydroxylabdanes[a]

	12	13	15a[b]	15b[b]
H-17a	4.54	4.39	4.40	4.72
H-17b	4.83	4.83	4.83	4.88

[a] At 60 MHz. [b] Quoted from ref 18.

Reaction of **12** with singlet oxygen gave the expected peroxide **13** in 54% yield whose NMR spectrum (see Experimental Section) was in accord with the proposed formula. Treatment of **13** with ferrous sulfate furnished the crystalline furan **14a**

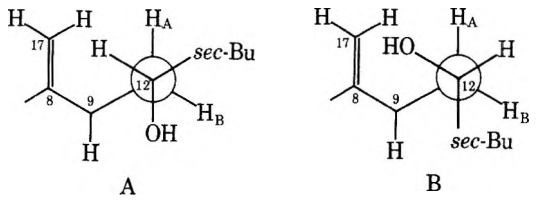


14a, R = Me, –OHβ (12*R*)
b, R = CO_2H, –OHβ (12*R*)
c, R = CO_2H, –OHα (12*S*)

15a, –OHβ (12*R*)
b, –OHα (12*S*)

in quantitative yield. The NMR spectrum of **14a** is presented in Table I together with spectra of the very similar labdanoic acids **14b** and **14c**.[17] The striking similarity between the NMR spectra of **14a** and **14b** (cf. shifts of H-17a and H-12) permits the deduction that the configuration of the new furan, and therefore that of **12** and **13**, at C-12 is *R*. Additional evidence is furnished by Table II in which the H-17 resonances of compounds **12** and **13** are compared with those of **15a** and **15b**.

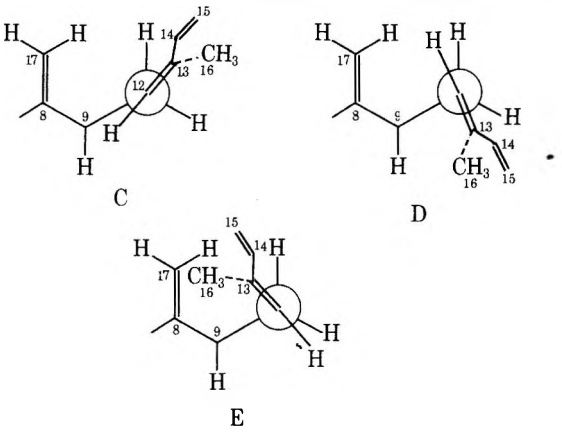
The coupling constants of H-12 in the NMR spectrum of



A B

14a are consistent with the contention[18] that in 12*R*-hydroxylabdanes conformation A is more highly populated than conformation B. The large coupling constant (J = 9 Hz) is expected for the anti arrangement of H-12 and H-11$_B$; the smaller one (3 Hz) is typical for the gauche relationship between H-12 and H-11$_A$.

The predominant formation of the 12*R* hydroperoxide in the reaction of **11** with singlet oxygen can be rationalized in a manner similar to that used to explain the preferred direction of nucleophilic attack on the ketone precursor **16** of **15a** and **15b**.[18] If eclipsed conformations of the isoprene moiety are excluded, three conformations, C, D, and E, are theoretically possible for **11**. But E can be ruled out because of severe interactions between either H-9 and H-16 or H-1 and H-16, even if there were considerable torsion around the 9,11 bond. In conformation C, H-17$_A$ shields C-12 from the left and attack by oxygen should occur only from the direction yielding the 12*R* hydroperoxide, whereas in conformation D the opposite situation prevails and formation of the 12*S* isomer would be expected. Preferential formation of **15a** by nucleophilic attack on **16** was rationalized[18] by noting that in the transition states the carbonyl oxygen is forced toward H-17$_A$ and that the transition state from D would be of higher energy than the transition state from C because of the smaller distance between H-17$_A$ and the oxygen atom. This effect should not be as pronounced in **11** as in **16** since C–H bonds are shorter than C=O. However, it should also be noted that C has the more favorable anti arrangement of the two large groups while D is gauche. Also D of **11** has an additional interaction between H-16 and H-9 not present in D of **16**.

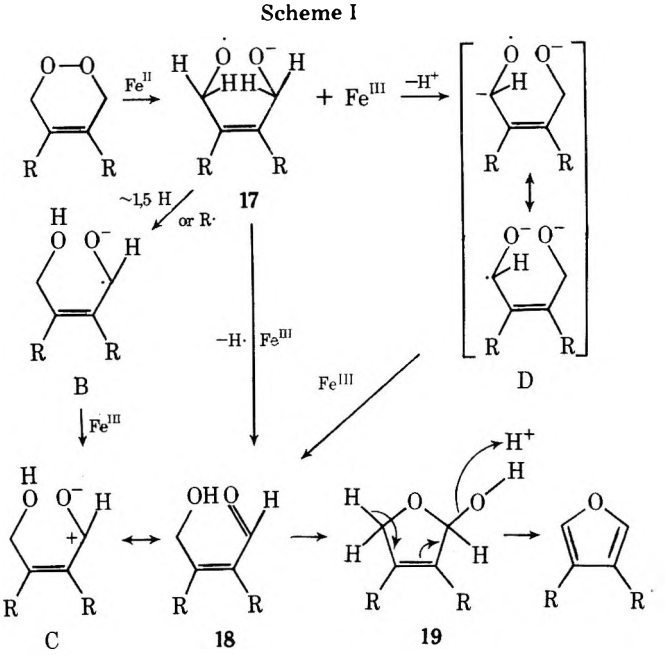


C D E

Discussion

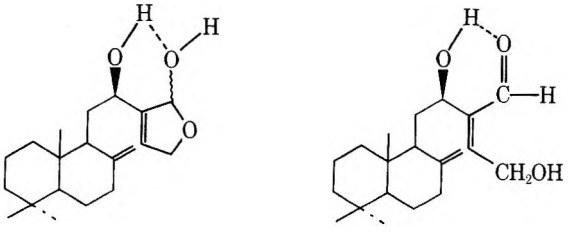
The mechanism by which furans are formed in one step and in excellent yield from 3,6-dihydro-1,2-dioxins by reaction with ferrous ion is probably analogous to the formation of hydroxy ketones in the phellandrene series.[3] Thus cleavage of the O–O bond would result in the radical anions **17** (Scheme I). Several possibilities exist for the conversion of **17** to final product. The most attractive one involves intramolecular hydrogen abstraction leading to anion radical B which is oxidized by Fe(III) to C equivalent to hydroxy aldehyde **18**. The latter is expected to cyclize to hemiacetal **19**. Loss of a proton from **17** and concomitant oxidation of the oxy radical [or more likely the allylic carbon radical by Fe(III)] to D followed by proton loss or fragmentation by loss of a hydrogen atom and oxidation would also furnish **18** but seems less plausible. It

Scheme I



should be noted that fragmentation by loss of H· and oxidation of the latter to H^+ is mechanistically equivalent to loss of H^+ and simultaneous oxidation of the radical. Hydrogen atom abstraction by another radical within the system is also a possibility; an example of this would be air oxidation of **17** to **18**. Dehydration of **18** to the furan is presumably catalyzed by either the Lewis acid Fe(III) or by a proton within the system. The reactions were usually worked up by extraction of an ethereal solution of the product mixture with dilute aqueous acid to facilitate removal of Fe(III) which is almost insoluble in neutral aqueous solution. However, dehydration of **19** does not occur during this procedure since TLC showed complete conversion to furan prior to workup.

An interesting observation was made in the preparation of **14a** from **13**. After addition of Fe(II) to **13**, TLC indicated complete disappearance of **13** and the formation of two new substances. One, less polar than **13**, was identified as **14a**; the second, more polar substance was converted completely to **14a** on stirring overnight. Hence the polar product was either the hemiacetal **20** or the hydroxyaldehyde **21**, both of which



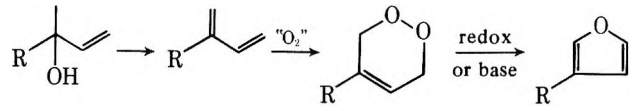
20 21

should be stabilized by hydrogen bonding. No attempt was made to isolate the intermediate since hemiacetals of type **19** (Scheme I) readily dehydrate upon chromatography.[7,19]

3,6-Dihydro-1,2-dioxins have served previously as starting materials for the preparation of substituted furans.[5,7,10,21,22] However, the yields of 3-substituted furans by the Fe(II) method are excellent, comparable to those obtained[22] by base-catalyzed rearrangement and dehydration of 3,6-dihydro-1,2-dioxins and superior to those achieved by thermal dehydration.[7,21] The one-step reaction is simple to carry out, is often complete on addition of Fe(II), and can be carried out in aqueous solvents in the presence of air. By-products were not observed. Use of the procedure is probably limited only by the availability of the appropriate diene and its ability to undergo the required Diels–Alder type reaction with singlet oxygen. As was mentioned earlier and was found in the case

of *trans*-biformene, dienes with trisubstituted double bonds can be expected to undergo preferentially an "ene" reaction.

The biogenetic implications of the formation of furans from acyclic dienes via peroxides have been noted[7,8,21] and demonstrated in biomimetic syntheses of naturally occurring furans.[7,21] Of particular importance is the circumstance that allylic alcohols coexist with dienes naturally (e.g., manool, the biformenes, and sclarene). Hence a possible biogenetic scheme for the formation of furans may be the following:



The redox system discovered in the course of this work is particularly attractive as a model for the last step in this scheme.

Experimental Section[23]

General Procedures. I. Photolyses. A. A solution of the olefin and sensitizer was irradiated in a Hanovia-type reactor using a Sylvania DVY-tungsten halogen projection lamp as an internal light source. The lamp was operated at 60–70 V and was cooled with a stream of air. A stream of oxygen was bubbled through the reaction mixture which was cooled by a water jacket between the lamp and the vessel containing the mixture.

B. A solution of the diene and *meso*-tetraphenylporphine in CCl_4 in a vessel cooled by a water jacket was irradiated with a 30-W sodium vapor lamp placed outside the vessel while oxygen was bubbled through the reaction mixture. These directions were supplied by Dr. Matsumoto.

C. A solution of the diene and sensitizer in a vessel surrounded by a water jacket was irradiated with a 150-W incandescent lamp placed near the vessel while oxygen was bubbled through the reaction mixture.

II. Reaction of Peroxides with $FeSO_4$. A solution of $FeSO_4 \cdot 7H_2O$ in distilled water was added all at once to a stirred solution of the peroxide in THF. Brown ferric salts precipitated immediately and the reactions were generally complete at this stage. The solvent was usually removed at reduced pressure, and the residue diluted with water and acidified to facilitate removal of the water-insoluble ferric salts. The mixture was extracted with ether and the washed and dried ether extracts removed to yield crude product.

Epidioxide of Myrcenol (3). This substance was prepared from myrcenol[24] by procedure A (solvent methylene chloride–5% methanol, sensitizer rose bengal[8]) and by procedure B. The reactions were run until TLC showed nearly complete consumption of starting material (usually 18–24 h). The rate of reaction was approximately the same by either procedure, but it was very difficult to remove the tetraphenylporphine used in procedure B. The crude mixture was evaporated to dryness and chromatographed over Florisil or silica gel. The product **3** was rechromatographed prior to further use.

Epidioxide of Epoxymyrcene (6). Epoxymyrcene (**5**) was prepared from β-myrcene by the literature method.[8] Procedures A and B were used with equal success; the sensitizer was separated from **6** by column chromatography.

5-(3-Furyl)-2-methylpentan-2-ol (4). A solution of 0.753 g of $FeSO_4 \cdot H_2O$ in 20 mL of water and 0.500 mg of **3** in 15 mL of THF was stirred for 2 h and worked up as described in the general reaction prccedure except that the reaction mixture was not acidified. Chromatography furnished 0.367 g (81%) of **4** (viscous liquid) which had an odor resembling that of myrcenol: IR bands at 3390, 1500, and 880 cm^{-1}; NMR signals at 7.25 t (J = 1.8 Hz) and 7.13 m (H-2′ and H-5′), 6.20 m (H-4′), 1.18 ppm (two superimposed methyl singlets). At 270 MHz, the H-5 signal was resolved into a triplet at 2.41 ppm (J = 7 Hz). For analysis, the product was repurified by preparative TLC.

Anal. Calcd for $C_{10}H_{16}O_2$: mol wt, 168.1149. Found: mol wt (MS), 168.1165.

2,3-Epoxy-5-(3′-furyl)-2-methylpentane (7). Reaction of 0.500 g of **6** and 0.700 g of $FeSO_4 \cdot 7H_2O$ in the manner described in the previous paragraph and chromatography of the crude product over 25 g of silica gel gave 0.418 g (92%) of **7** as a volatile liquid homogeneous on TLC, which had IR bands at 3125–3090, 1550, and 880 cm^{-1}; NMR signals at 7.36 t (J = 1.7 Hz) and 7.27 m (H-2′ and H-5′), 6.29 m (H-4′), 2.77 t (J = 6 Hz, H-3), 2.63 t (somewhat distorted, J = 7 Hz, H-5), 1.83 c (H-4), 1.30 and 1.20 ppm (two methyl singlets).

Anal. Calcd for $C_{10}H_{14}O_2$: mol wt, 166.0993. Found: mol wt (MS), 166.1004.

Dehydration of Manool. 8, 11, and *cis*-biformene were prepared from manool and separated by the procedure of Carman and Dennis.[11]

15,16-Epidioxy-8(17),13-labdadiene (9). This peroxide was prepared from 0.550 g of sclarene by procedure A (solvent 250 mL of CH_2Cl_2–5% methanol, sensitizer 20 mg of rose bengal, time 24 h). Analytical TLC of the mixture showed complete reaction, with one major spot and a more polar streak. The solvent was removed at reduced pressure; the residue was taken up in $CHCl_3$, filtered, and evaporated. Preparative TLC of the crude product (solvent 1:19 ether–hexane) gave 177 mg (29%) of **9** which crystallized on drying. Further purification by preparative TLC raised the melting point to 37–39 °C; IR bands at 3070 and 1638 cm^{-1}; NMR signals at 5.62 m (H-14), 4.82 br ($W_{1/2}$ = 4 Hz), and 4.56 br (H-17), 4.47 c (4 protons, H-15 and H-16), and 0.87, 0.80, and 0.68 ppm (C-4, C-10 methyls).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.00; H, 10.43.

In another run, 0.500 g was oxygenated for only 15 h. Chromatography gave 150 mg of sclarene and 157 mg of **9** (28%, but 40% based on recovered diene).

15,16-Epoxy-8(17),13(16),14-labdatriene (*anti*-Daniellane, 10a). Reaction of 0.100 g of **9** in 10 mL of THF with 0.100 g of $FeSO_4 \cdot 7H_2O$ in 8 mL of water was slow, presumably because of the low solubility of **9** in the aqueous medium. TLC showed complete reaction after 1 h. The mixture was not acidified. The crude residue obtained after the usual workup was chromatographed over 20 g of silica gel: yield 93 mg (99%) of **10a**; IR bands at 3050, 1635, 1495, and 874 cm^{-1}; NMR signals at 7.31 t (J = 1.8 Hz) and 7.17 m (H-15 and H-16), 6.23 m (H-14), 4.84 br ($W_{1/2}$ = 4 Hz) and 4.55 br ($W_{1/2}$ = 4 Hz, H-17), 0.86, 0.79, and 0.68 ppm (C-4 and C-10 methyls). The analytical sample was repurified by preparative TLC.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.76; H, 10.55.

8(17),13(16),14-Labdatrien-(12*R*)-ol (12). Reaction of 0.550 g of *trans*-biformene with singlet oxygen by procedure A (solvent CH_2Cl_2–5% methanol, sensitizer 20 mg of rose bengal). After 2.5 h, 0.4 g of $P(OEt)_3$ was added and the solvent was removed at reduced pressure. The residue was purified by preparative TLC (eluent 1:9 ether–hexane). The least polar band (30 mg) was a mixture (TLC and NMR); a more polar band (101 mg), while chromatographically pure, was also a mixture by NMR criteria. These fractions were not examined further nor was a highly polar band containing $P(OEt)_3$ and other materials. A chromatcgraphically pure band of intermediate polarity which was pure by NMR criteria was isolated as a gum (**12**): wt 226 mg (43%); IR bands at 3410, 3049, and 1628 cm^{-1}; NMR signals at 6.34 dd ($J_{14,15trans}$ = 18, $J_{14,15cis}$ = 11 Hz, H-14), 5.37 dbr (J = 18 Hz, H-15 trans to H-14), 5.08 dbr ($J \sim 11$ Hz, H-15 cis to H-14), 5.18 d and 5.10 d (J = 1 Hz, H-16), 4.83 br and 4.50 br (H-17), 4.38 m (H-12), 0.87, 0.79, 0.67 ppm (C-4 and C-10 methyl). Elemental analyses of this substance were not satisfactory owing to rapid decomposition; consequently it was prepared and purified just before use.

15,16-Epidioxy-8(17),13-labdadien-(12*R*)-ol (13). The reaction of 1.35 g of freshly purified **12** with singlet oxygen was carried out by procedure A (solvent CH_2Cl_2–5% methanol, sensitizer 20 mg of rose bengal) for 20 h when TLC showed the pressure of some starting material, but only one major product and small amounts of more polar fractions. The crude product was chromatographed over 100 g of silica gel; this resulted in recovery of 233 mg of **12** and isolation of 813 mg of **13** (54%, 64% based on recovered starting material) as a gum which was further purified by preparative TLC; IR bands at 3440, 3068, and 1638 cm^{-1}; NMR signals at 5.81 m (H-14), 4.83 br and 4.39 br (H-17), 4.56 m (H-15 and H-16), 4.14 m (H-12), 0.87, 0.80, and 0.66 ppm (C-4 and C-10 methyls).

Anal. Calcd for $C_{20}H_{32}O_3$: mol wt, 320.2334. Found: mol wt (MS), 320.2338.

15,16-Epoxy-8(17),13(16),14-labdatrien-(12*R*)-ol (14). After reaction of 0.100 g of **13** in 15 mL of THF with 90 mg of $FeSO_4 \cdot 7H_2O$ in 10 mL of water for 1 h, TLC indicated complete disappearance of **13** and formation of a less polar spot (**14**) and more polar material, presumably **26** or **27**. After stirring overnight, only the spot corresponding to **14** remained and had increased in intensity. After the usual workup there was obtained 99 mg of solid. Recrystallization from pentane afforded 88 mg (93%) of **14**: mp 71–72 °C; IR bands at 3415, 3125, 3113, 3062, 1635, 1500, and 872 cm^{-1}; NMR signals (270 MHz) at 7.32 d (J = 1.6 Hz, H-15 and H-16), 6.36 t (J = 1.6 Hz, H-14), 4.85 br and 4.47 br (H-17), 4.60 dd (J = 9, 3 Hz after D_2O exchange, H-12), 0.88, 0.81, and 0.68 ppm (C-4 and C-10 methyls).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.64; H, 10.21.

Registry No.—**3**, 57073-98-0; **4**, 61597-51-1; **5**, 29414-55-9; **6**, 56764-67-1; **7**, 61597-52-2; **8**, 511-02-4; **9**, 61597-53-3; **10a**, 61597-54-4; **11**, 10395-42-3; **12**, 61618-20-0; **13**, 61604-71-5; **14a**, 61597-55-5; myrcenol, 543-39-5; $FeSO_4$, 19468-88-3.

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(1) Supported in part by a grant from the National Science Foundation (GP-12582).
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(9) We wish to thank Dr. Matsumoto for supplying us with details on these reactions.
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(17) R. A. Bell, M. B. Gravestock, and V. Y. Taguchi, *Can. J. Chem.*, **50**, 3749 (1972).
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(23) Experimental details have been specified in ref 2.
(24) We wish to thank Dr. F. L. Pickard, Union Camp Corp., for a gift of β-myrcene and Dr. W. I. Taylor, International Flavors and Fragrances, Inc., for a gift of myrcenol.

Nitrones. 4.[1] Reactions of Δ^1-Pyrroline *N*-Oxides with Phosphonates. Alternative Formation of Aziridines and Enamines[2]

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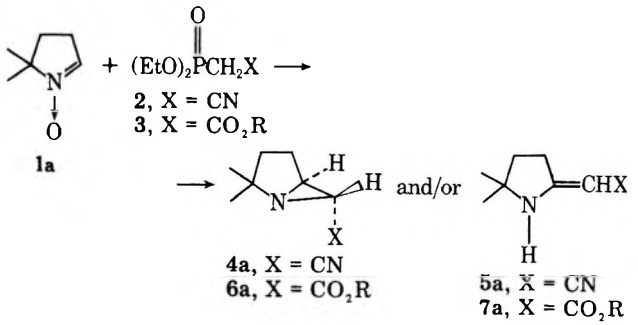
Variously methylated derivatives of Δ^1-pyrroline *N*-oxide (**1**) were reacted with diethyl cyanomethylphosphonate (**2**) and dialkyl alkoxycarbonylphosphonates **3** using sodium hydride in 1,2-dimethoxyethane or alkali metal alkoxides in alcoholic solvents. These reactions were shown to lead to 6-*exo*-cyano- and 6-*exo*-alkoxycarbonyl-1-azabicyclo[3.1.0]hexane derivatives **4** and **6**, or alternatively 2-cyanomethylene- or 2-alkoxycarbonylmethylenepyrrolidine derivatives **5** and **7**. This work describes the influence of substitution in the pyrroline *N*-oxide and of the variations in the reagents and solvents on the ratio of the products obtained in the reactions. It was found that when the reactions were carried out in 1,2-dimethoxyethane, the major product obtained was of aziridinic structure. However, using alcoholic solvents the yield of the enaminic products increased at the expense of the aziridinic products with increasing acidity of the solvent. The influence of the alkali metal cations on the course of the reaction was also studied, and it was found that lithium *tert*-butoxide promotes the formation of enaminic products as compared to sodium and potassium *tert*-butoxides.

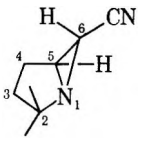
Previously we reported that the reactions of 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**1a**) with diethyl cyanomethylphosphonate (**2**) and triethyl phosphonoacetate (**3**, R = C_2H_5) may be directed to lead to aziridines or enamines.[3,4] In this paper we wish to describe in detail the influence of substitution in the substrate and the variations in the reagents and reaction conditions on the course of this novel reaction.



Results

The results from the reactions of a series of Δ^1-pyrroline *N*-oxides **1** with diethyl cyanomethylphosphonate (**2**) and dialkyl carbalkoxymethylphosphonate **3** are listed in Tables I–III. All reactions were monitored by thin layer chromatography and, when they resulted in the formation of more than one product, the mixtures were separated by chromatography. The identification of products is mainly based on their NMR spectra. Therefore it is of interest to present the significant features in the spectra of representative compounds.

The NMR spectrum of 6-*exo*-cyano-2,2-dimethyl-1-azabicylo[3.1.0]hexane (**4a**) shows the angular aziridinic hydrogen



4a

H-5 as a broad signal at δ 2.80 ppm and the second aziridinic hydrogen (H-6) as a doublet at higher field, namely at δ 1.94 ppm (J = 2.5 Hz).

We have previously suggested[5] that H-6 appears at higher field because of the shielding influence of the cis-related *N*-alkyl substituent. This assignment was subsequently confirmed by preparation of the 6-endo-deuterio derivative of **4a** using diethyl cyanomethylphosphonate-d_2. The coupling constant of H-6 indicates trans-aziridinic structure.[6]

Table I. Results from the Reactions of Diethyl Cyanomethylphosphonate (2) with Δ¹-Pyrroline *N*-Oxide Derivatives

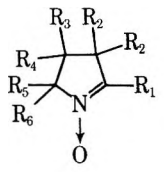
No.	Nitrone	Base	Solvent	Temp, °C	Time, h	Products: Aziridine	(yield, %)	Enamine	(yield, %)
1[a]	1a	NaH	DME	25	3	4a	(32)		(0)
2	1a	NaO-*t*-Bu	*t*-BuOH	40	3	4a	(59)	5a	(21)
3	1a	NaOEt	EtOH	25	21		(0)	5a	(95)
4	1a	NaOMe	Pentane	25	3	4a	(6)	5a	(80)
5[b]	1b	NaH	DME	25	24	4b + 4c	(20)	5b	(10)
6	1b	NaO-*t*-Bu	*t*-BuOH	Reflux	24	4b + 4c	(56)	5b	(25)
7	1b	NaOEt	EtOH	25	5		(0)	5b	(95)
8	1d	NaH	DME	Reflux	24	4d	(22)		(0)
9	1d	NaO-*t*-Bu	*t*-BuOH	Reflux	48	4d	(16)		(0)
10	1d	NaOEt	EtOH	Reflux	48	No reaction			
11	1d	NaOMe	MeOH	Reflux	48	No reaction			
12	1e	NaH	DME	25	48	4e	(18)	5e	(40)
13	1e	NaO-*t*-Bu	BuOH	40	24	4e	(26)	5e	(38)
14	1e	NaOEt	EtOH	25	24		(0)	5e	(40)
15	1f	NaH	DME	Reflux	48	No reaction			

[a] This experiment was first carried out by J. Pesso. [b] This experiment was first carried out by H. Sofer.

Table II. Results from the Reactions of Phosphonoacetates 3 with Δ¹-Pyrroline *N*-Oxides Derivatives[a]

No.	Nitrone	Base	Solvent	Time, h	Products: Aziridine	(yield, %)	Enamine	(yield, %)
1[b]	1a	NaH	DME	24	6a	(35)		(0)
2	1a	*t*-BuONa	*t*-BuOH	24	6a[c]	(75)		(0)
3	1a	EtONa	EtOH	24	6a	(15)	7a	(32)
4	1a	MeONa	MeOH	24	6a	(6)	7a	(36)
5	1b	NaH	DME	24	6b[d] + 6c[d]	(24)	7b	(11)
6	1b	*t*-BuONa	*t*-BuOH	24	6b[c] + 6c[c]	(38)	7b[e]	(46)
7	1b	EtONa	EtOH	24	6b + 6c	(27)	7b	(35)
8	1b	MeONa	MeOH	24		0	7b	(31)
9	1d	NaH	DME	120	6g + 6h	(30)		(0)
10	1d	*t*-BuONa	*t*-BuOH	96	6g[c] + 6h[c]	(40)		(0)
11	1d	EtONa	EtOH	48	No reaction			
12	1d	MeONa	MeOH	48	No reaction			
13	1e	NaH	DME	48	6e	(34)		(0)
14	1e	*t*-BuONa	*t*-BuOH	48	6e[f]	(35)		(0)
15	1e	EtONa	EtOH	48	No reaction			
16	1e	MeONa	MeOH	48	No reaction			

[a] All reactions were carried out in refluxing solvents. [b] This experiment was first carried out by S. Levi. [c] Contaminated by *tert*-butyl ester as evidenced by NMR. [d] The two isomers were present in the ratio of 45:55. [e] Separated by TLC to **7b**, R = Et (25%), and R = *t*-Bu (21%). [f] Separated by GLC to **6e**, R = Et and R = *t*-Bu (1:1).



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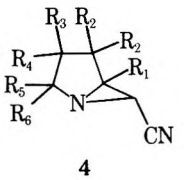

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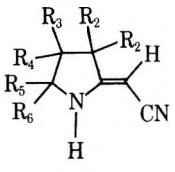

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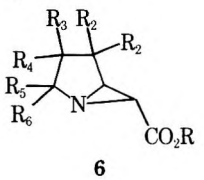

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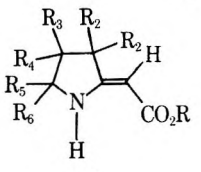
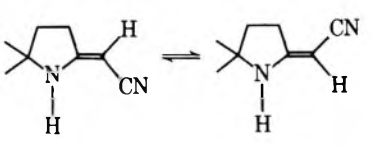


7

a, $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = R_6 = CH_3$
b, $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = R_6 = CH_3$
c, $R_1 = R_2 = R_4 = H$; $R_3 = R_5 = R_6 = CH_3$
d, $R_1 = R_3 = R_4 = CH_3$; $R_2 = R_5 = R_6 = H$
e, $R_1 = R_3 = R_4 = H$; $R_2 = R_5 = R_6 = CH_3$
f, $R_1 = R_5 = R_6 = CH_3$; $R_2 = R_3 = R_4 = H$
g, $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = R_5 = CH_3$
h, $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = R_6 = CH_3$

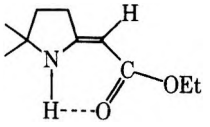
The enaminic derivatives also show characteristic NMR spectra. Enamino nitrile **5a** shows the NH signal at δ 5.80 ppm



5a **5e**

and two signals at δ 3.85 and 3.55 of ½ H each that may be assigned as belonging to the vinylic H, indicating the existence of equilibrium in solution.

In contrast, enamino ester **7a** shows the NH at a much lower field, namely at δ 7.70 ppm, presumably due to intramolecular hydrogen bonding with the ester oxygen, and the vinylic proton at δ 4.36 ppm as a singlet. These are in good agreement with the NMR data obtained by Eschenmoser and co-workers for 2-*tert*-butoxycarbonylmethylenepyrrolidine.[7] The vinylic protons as well as the NH protons of both types of enamines **5** and **7** exchange with D upon the addition of D_2O. Enamino



7a

Table III. Effect of Metal on the Reaction of Δ¹-5,5-Dimethylpyrroline *N*-Oxide (1a) with Phosphonates in *tert*-Butyl Alcohol

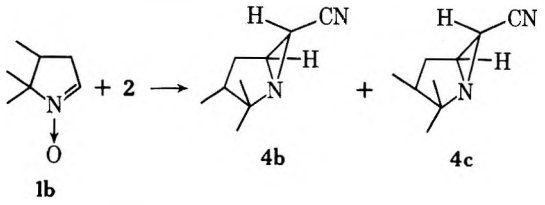
	M	Phosphonate	Temp, °C	Time, h	Products: Aziridine	Yield, %	Enamine	Yield, %
1	Li	2	40	3	4a	20	5a	80
2	Na	2	40	3	4a	59	5a	21
3	K	2	40	3	4a	41	5a	51
4	Li	3[a]	Reflux	24	6a[b]	61	7a[b]	34
5	Na	3[a]	Reflux	24	6a[b]	75	7a	0
6	K	3[a]	Reflux	24	6a[b]	75	7a	0

[a] R = C_2H_5. [b] These products were contaminated by the corresponding *tert*-butyl ester presumably resulting from transesterification during the reaction.

nitrile **5a** shows in the infrared spectrum an absorption band at 2180 cm^{-1}, also confirming the enamino nitrile structure.[8]

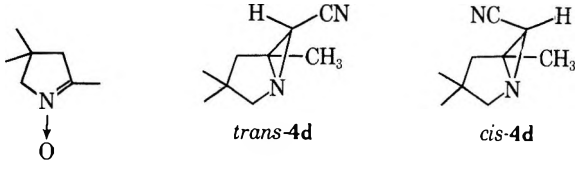
Examination of the results listed in Table I reveals that the reactions of pyrroline *N*-oxides with phosphonate **2** show marked dependence on the reaction conditions. By comparing reactions 1–3 in Table I, it is seen that while using NaH/DME only the formation of aziridine **4a** is observed, the use of *tert*-butyl alcohol already causes the formation of some enamine **5a**, and in ethanol only the latter is formed. Sodium methoxide in an inert solvent leads mainly but *not exclusively* to the formation of enamine. A similar trend is apparent on comparing reactions 5–7 and reactions 12–14 in Table I.

The reaction of 4,5,5-trimethylpyrroline *N*-oxide (**1b**) with **2** afforded the stereoisomeric aziridines **4b** and **4c** in approximately equal amounts as demonstrated by GLC.



1b **4b** **4c**

Reaction of keto nitrone **1d** with **2** cannot give enaminic product. The product obtained in these reactions (entries 8 and 9, Table I) showed in the NMR spectrum in $CDCl_3$ the aziridinic H as a singlet at 2.20 ppm. On the basis of this, it is impossible to distinguish between the two possible aziridines **4d**. We have attempted to do so by measuring aromatic solvent

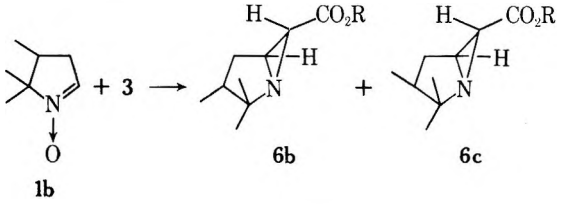


1d *trans*-**4d** *cis*-**4d**

induced shifts (ASIS) in the NMR spectra;[9] however, in contrast to other systems,[1,5,9] we found that all hydrogens of a representative compound of this series (see Experimental Section for the NMR spectra of **4a**) suffer an upfield shift upon passing from chloroform to benzene, rendering this approach unsuitable for the solution of such problems in this system. It should be emphasized that keto nitrone **1d** reacted with **2** only with NaH/DME and with NaO-*t*-Bu in *t*-BuOH but not with sodium alkoxides in ethanol and methanol (Table I, entries 10 and 11). In these reactions unreacted starting materials were recovered. In contrast to **1d**, keto nitrone **1f** did not react with **2** even with NaH/DME.

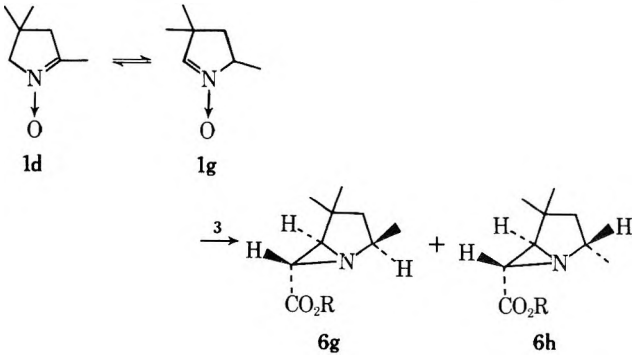
The results from the reaction of the nitrones **1** with phosphonoacetates **3** are listed in Table II. From the examination of this table, it is apparent that the reactions of the phosphonoacetates require more drastic conditions than those of the cyanomethylphosphonate. All the reactions of the phosphonoacetates were carried out in refluxing solvents for 24 h or more, in contrast to the cyanomethylphosphonate which reacted with the more reactive nitrones at room temperature within a few hours. Another general feature worthy of note is the decreased tendency of the phosphonoacetates, as compared to the cyanomethylphosphonates, to form enaminic products.

Similar to the reactions of cyanomethylphosphonate, we can see in the reactions listed in Table II variations in the product ratio with change of solvent. While the reaction of nitrone **1a** with phosphonate **3** (R = OEt) leads exclusively to aziridinic product **6a** when carried out with NaH in DME or with NaO-*t*-Bu in *t*-BuOH, increasing amounts of enamino ester **7a** are formed in ethanol and methanol (entries 1–4, Table II). Similar trends can be seen in the reactions of the trisubstituted nitrone **1b** (entries 5–8, Table II). Examination of the aziridinic fraction obtained from the reactions of **1b** and **3** by GLC revealed that, as in the reactions of **1b** and **2**, a mixture of stereoisomers **6b** and **6c** is obtained. The composition of the mixture is approximately 60:40. However, it is not known which isomer is in excess.



1b **6b** **6c**

The reaction of keto nitrone **1d** with phosphonoacetate **3** (R = Et) proceeds in a different way than that with cyanomethylphosphonate **2**. While the reaction of the latter afforded the expected aziridinic product **4d**, as evidenced by the appearance of the aziridinic hydrogen as a singlet, the NMR spectrum of the aziridinic product from this reaction showed two doublets at δ 2.55 and 1.88 ppm (J = 2.5 Hz) characteristic of trans-2,3-disubstituted aziridines. On the basis of this NMR spectrum and GLC analysis, we assume that the product of this reaction is a mixture of stereoisomers **6g** and **6h** that are formed from nitrone **1d** via its tautomer **1g**. Reactions of the

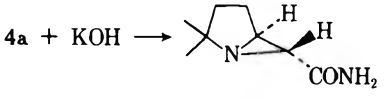


1d **1g** **6g** **6h**

tetrasubstituted aldonitrone **1e** with **3** led only to aziridine **6e**, and significantly, neither **1d** nor **1e** reacted with phosphonate **3** in ethanol or in methanol.

In Table III, there are listed a series of reactions of phosphonates **2** and **3** with a representative nitrone **1a** with three alkali metal *tert*-butoxides. Comparison of the first three entries in this table reveals that enamine formation is maximal when M = Li, decreases with M = Na, and increases again using K. From entries 4–6 it is again clear that the formation of enaminic product can be optimized using lithium.

In separate control experiments, we have ascertained that (1) nitrone **1a** can be recovered unchanged from a solution of sodium ethoxide in ethanol; (2) aziridinic ester **6a** is also stable in a solution of sodium ethoxide in ethanol; (3) treatment of cyanoaziridine **4a** with sodium ethoxide in ethanol results in the formation of **6a** but not **5a** or **7a**. Another example for the base stability of the 1-azabicyclo[3.1.0]hexane system is provided by the hydrolysis of **4a** to aziridinic amide **8** using potassium hydroxide in *tert*-butyl alcohol.

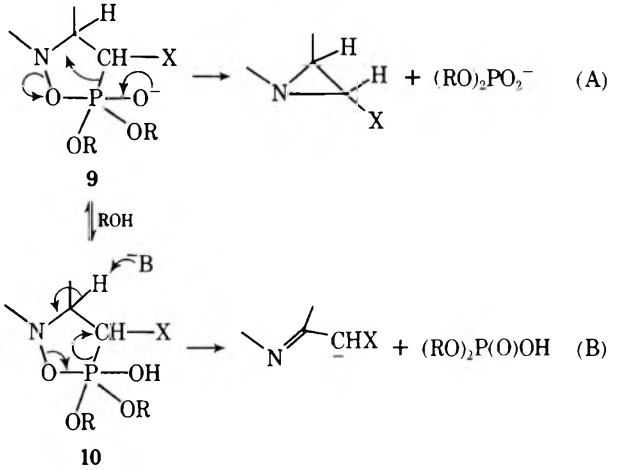


8

Discussion

The results of the control experiments described clearly indicate that the aziridinic and enaminic products formed in these reactions are not interconvertible under the reaction conditions. Therefore, it follows that the two types of products are formed by two different routes.

In our preliminary communication,[3] we have put forward the suggestion that the reaction between nitrones and phosphonates leads first to an oxazaphospholidine **9**, which may give rise to the aziridine by pathway A. Such fragmentation is presumably facilitated by back-donation from the negatively charged exocyclic oxygen.

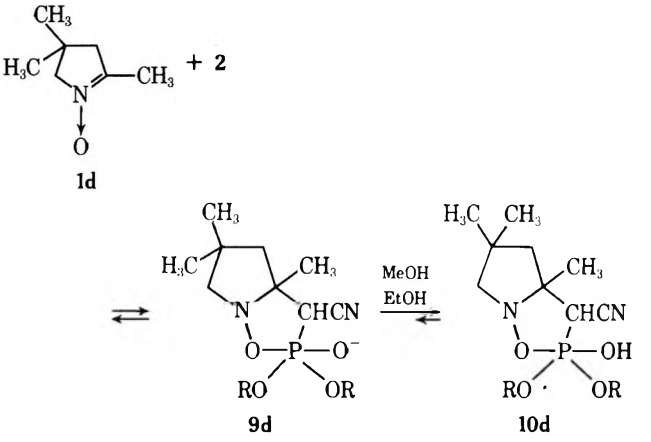


In the presence of protic solvents the negatively charged oxygen in **9** is protonated resulting in the formation of **10**. This intermediate may undergo a different type of base-catalyzed fragmentation to yield the corresponding enamine derivative (eq B). Therefore, it can be expected that the more acidic is the solvent the more will the formation of the aziridinic product be inhibited by protonation. These suggestions are supported by the experimental results.

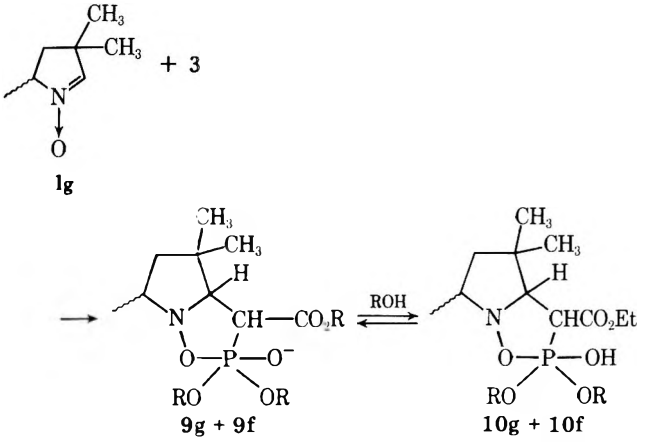
The proportion of the enaminic product increases in the order methanol > ethanol > *tert*-butyl alcohol, which is also the order of acidities of these alcohols[10] (see Table I, entries 2, 3; 6, 7; 13, 14; and Table II, entries 2–4, 6–8).

The inhibitory influence of the protic solvent upon the formation of aziridine can be seen in several examples. The reaction of keto nitrone **1d** cannot lead to enaminic product. This nitrone reacts with **2** to give aziridine **4d** in the presence of NaH/DME or NaO-*t*-Bu in *t*-BuOH. However, in the more acidic solvents, ethanol and methanol, no products are formed (Table I, 8–11).

This presumably indicates that in the more acidic solvent, the decomposition of **9d** is inhibited by its conversion to the protonated **10d**. Similar conclusions can be drawn from the



behavior of **1d** toward phosphonate **3** (Table II, 9–12). The behavior of this nitrone in its reactions with **3** could be rationalized by assuming the existence of the tautomeric equilibrium between **1d** ⇄ **1g**. We have previously observed[11] that the reaction of triethyl phosphonoacetate with a nitrone of low reactivity may lead to the formation of products via a less stable but more reactive tautomer.[12] Reaction of nitrone **1g** with **3** should lead to **9g** which may decompose to aziridines **6g** and **6f** by mechanism A. However, in the more acidic solvents, methanol and ethanol, the protonated **10g** and **10f** are obtained which cannot decompose to aziridines. Base-catalyzed fragmentation of **10g** + **10f** to enamine **7g** according to

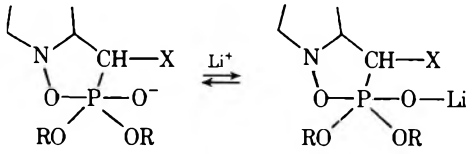


mechanism B is apparently inhibited by the two geminal methyl groups that hinder the approach of base to remove the proton from position 2. Similar behavior is exhibited by nitrone **1e** (Table II, 13–16).

The role played by base in the formation of enamines is demonstrated by experiment 4 in Table I. The high yield of enamine (80% as compared to aziridine 6%) in this experiment demonstrates the kinetic difference between the two modes of fragmentation. In the absence of protic solvent aziridine formation is not inhibited by protonation and both products result from intermediate **9**.

Another aspect is the effect of cation on the course of the reaction. The effect of cation, particularly lithium, upon the steric course of the Wittig reaction[13] and upon the Horner–Emmons[14] reactions has been demonstrated. We found that varying the cation has no effect on the stereochemistry of the products. However, we found, as indicated by the results in

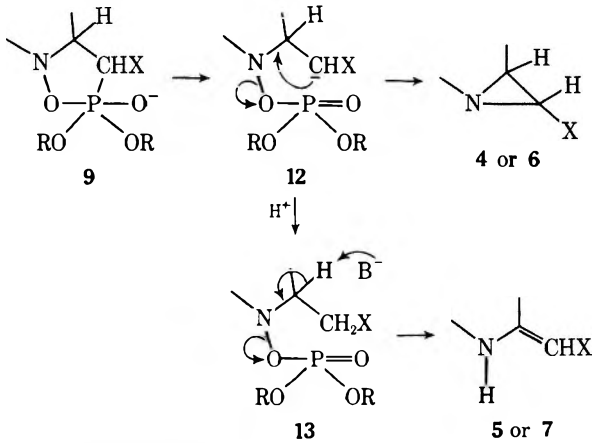
Table III, that change of the cation influences the aziridine: enamine ratio. The difference between the product ratio in reactions 2 and 3 in Table III can presumably be accounted for by the difference in basicities between sodium and potassium *tert*-butoxides. However, a different explanation is needed for the effect of lithium. It has been pointed out[15] that anomalous properties of lithium result mainly from the small size of the atom and of the ion. The polarization power of lithium cation is the greatest of all the alkali metal ions and leads to a singularly great tendency toward covalent bond formation. Consequently it is reasonable to assume that the formation of increased amounts of enaminic products in the presence of lithium is the result of inhibition of the decomposition of intermediate **9** to aziridine, by covalent bond formation between lithium and the negatively charged oxygen.



9 **11**

We have noted throughout this work (Tables I–III) and previously[1,3] the greater tendency to form enamines with the cyanophosphonate **2** than with phosphonoacetates **3.** It may be assumed that the stronger electron-withdrawing properties of the cyano group as compared to those of the carbethoxy group cause more P–C bond breaking in intermediate **9**, X = CN, then when X = CO_2Et, resulting in the formation of **12.**

This carbanion may undergo an S_Ni type reaction leading to aziridine, or protonation to **13,** followed by β-elimination to enamine. The effect of the nature of substituent X upon these two competing reactions of **12** has been discussed in terms of perturbation theory in our previous paper.[1]



9 **12** **4 or 6**

13 **5 or 7**

Throughout this work and in our previous communications[1,3,11] we noted that the reactions of nitrones with phosphonates studied lead stereoselectively to trans aziridines. In this respect this reaction resembles the "modified Wittig" reaction[16] that leads preferentially to trans olefins. At the present, it seems reasonable to assume that, as in the case of the trans-olefin synthesis, the stereoselectivity of our reaction is a result of thermodynamic control upon the reversible formation and interconversion of the two possible diastereomeric erythro and threo reaction intermediates.

Experimental Section[17]

Starting Materials. Nitrones[18,19] and phosphonates[20] were prepared according to the literature. Diethyl cyanomethylphosphonate-d_2 was prepared by dissolving **2** in D_2O for 2 days and extracted with chloroform. This procedure was repeated four times.

General Procedure for Reactions in Dimethoxyethane. A 50% dispersion of sodium hydride in mineral oil (0.5 g, 0.01 mol) was washed with petroleum ether (bp 40–60 °C) (3 × 10 mL) in an inert atmosphere. After evaporation of the residual petroleum ether, 10 mL of DME (freshly distilled from lithium aluminum hydride) was injected, followed by 0.01 mol of diethyl cyanomethylphosphonate (**2**) or diethyl carboalkoxymethylphosphonate **3** dissolved in 5 mL of DME with cooling. After the liberation of hydrogen ceased 0.01 mol of the corresponding Δ^1-pyrroline *N*-oxide **1** dissolved in 5 mL of DME was introduced. The reaction mixture was stirred under the conditions (time and temperature) indicated in the tables. DME was evaporated in vacuo and the products were isolated as described below. The yields are given in tables.

General Procedure for the Reactions with Sodium Alkoxide in Alcohol. Sodium (0.23 g, 0.01 mol) was dissolved in 10 mL of dry alcohol ROH (R = *t*-Bu, Et, Me) in an inert atmosphere (in case of R = *t*-Bu about 9 h of reflux was needed). After the formation of the alkoxide, 0.01 mol of **2** or **3** dissolved in 5 mL of ROH was injected [the reactions in *tert*-butyl alcohol and ethanol were run using **3** (R = Et) while for those in methanol **3** (R = Me) was used], followed by a solution of 0.01 mol of the corresponding Δ^1-pyrroline *N*-oxide **1** in 5 mL of ROH. The reaction mixture was stirred under the conditions (time and temperature) indicated in tables. After evaporation of the alcohol in vacuo the products were isolated as indicated below. The yields are given in the tables.

Reactions of 1a with Phosphonates 2 and 3 with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. To a solution of 0.56 g (0.005 mol) of freshly sublimed potassium *tert*-butoxide in 10 mL of dry *tert*-butyl alcohol in an inert atmosphere was injected 0.585 g (0.005 mol) of **2** or 1.12 g (0.005 mol) of **3** (R = Et) dissolved in 2 mL of *tert*-butyl alcohol, followed by a solution of 0.565 g (0.005 mol) of 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**1a**) in 3 mL of *tert*-butyl alcohol. The reaction mixtures were stirred under the conditions (time and temperature) indicated in Table III. After evaporation of *tert*-butyl alcohol the isolation of the products was carried out in the usual way. The yields are given in Table III.

Reactions of 1a with Phosphonates 2 and 3 with Lithium *tert*-Butoxide in *tert*-Butyl Alcohol. To a solution of lithium *tert*-butoxide prepared by injection of 0.144 g (0.96 mL, 0.00225 mol) of 15% w/v *n*-butyllithium in hexane to 10 mL of dry *tert*-butyl alcohol was added a solution of 0.398 g (0.00225 mol) of **2** or 0.504 g (0.00225 mol) of **3** (R = Et) in 3 mL of *tert*-butyl alcohol followed by a solution of 0.254 g (0.00225 mol) of 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**1a**) in 2 mL of *tert*-butyl alcohol. The reaction mixtures were stirred under the conditions (time and temperature) indicated in Table III. After evaporation of the *tert*-butyl alcohol, the products were isolated, as indicated below. The yields are given in Table III.

Reaction of 1a with 2 with Sodium Methoxide in Pentane. To a solution of 0.27 g (0.005 mol) of sodium methoxide in 20 mL of dry pentane (freshly distilled from phosphorus pentoxide) in an inert atmosphere was added 0.885 g (0.005 mol) of **2** followed by 0.565 g (0.005 mol) of **1a,** and the reaction mixture was stirred under the conditions (time, temperature) indicated in Table I. After evaporation of pentane the products were isolated as usual. The yields are given in Table I.

Control Experiments. A. Nitrone **1a** (0.113 g, 0.001 mol) which was recovered after stirring in an inert atmosphere for 2 h at room temperature in a solution of sodium ethoxide prepared by dissolving 0.03 g (0.0013 mol) of sodium in dry ethanol (1.5 mL) was found to be identical with unreacted **1a.**

B. Aziridine **4a** (0.136 g, 0.001 mol) was kept in an inert atmosphere for 2 h at room temperature in a solution of sodium ethoxide prepared by dissolving 0.03 g (0.0013 mol) of sodium in dry ethanol (1.5 mL). Examination of the products by NMR and thin layer chromatography indicated the presence of starting material **4a** in addition to **6a,** and the complete absence of **5a** and **7a.**

C. Hydrolysis of 4a with Potassium Hydroxide. A solution of 0.136 g (0.001 mol) of **4a** and potassium hydroxide (0.066 g, 0.0013 mol) in 2 mL of *tert*-butyl alcohol was warmed on a water bath for a few seconds and left to stand overnight at room temperature. After evaporation of the solvent, the residue was taken up in chloroform–petroleum ether (3:2) and passed through a short alumina column. Recrystallization from chloroform–ether (1:1) gave 0.15 g of 2,2-dimethyl-1-azabicyclo[3.1.0]hexane-*exo*-6-carboxamide (**8**): mp 148–149 °C; IR (Nujol) 3300, 3140, 1730 cm^{-1}; NMR ($CDCl_3$) δ 6.45 2 H bs, 2.45 1 H m, 2.28–1.80 2 H m, 2.01 1 H d (J = 2.5 Hz), 1.50–0.98 8 H m; mol wt calcd, 154, found (MS) m/e 154, 110 (M − $CONH_2$).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.33; H, 9.09; N, 18.18. Found: C, 61.96; H, 9.12; N, 18.20.

Isolation of Products. Reactions were followed by thin layer

chromatographic analysis using plates of alumina G.F.$_{254}$ of 0.25-mm thickness. The residues obtained from the reactions after evaporation of the solvent were chromatographed on short columns of neutral alumina (70 g for a reaction on a 0.01 molar scale) to remove the diethylphosphate, followed by preparative thin layer chromatography (alumina G.F.$_{254}$, 1 mm) in those cases where both enaminic and aziridinic products were formed. The solvents used for elution of columns and development of plates ranged from chloroform to chloroform–petroleum ether (bp 40–60 °C) (1:3). In the ester series, the aziridines **6** were found to be more polar than the respectives enamines **7**, which contrasts to the nitrile series in which the aziridines **4** were less polar than the corresponding enamino nitriles **5**. Extraction of the compounds from the alumina in the preparative thin layer chromatographic separations was effected by boiling chloroform. We found that the recovery of the products from the alumina can be considerably improved by immersion of the suspension of alumina in chloroform in an "ultrasonic bath" for a few minutes.

***exo*-6-Cyano-2,2-dimethyl-1-azabicyclo[3.1.0]hexane (4a):** bp 77–90 °C (0.2 mm); mp (from petroleum ether) 77–78 °C; IR (Nujol) 2240 cm^{-1}; NMR ($CDCl_3$) δ 2.80 1 H m, 2.33–2.03 2 H m, 1.94 1 H d (J = 2.5 Hz), 1.45–1.00 2 H m, 1.26 3 H s, 1.17 3 H s; (C_6D_6) δ 2.27 1 H m, 1.70–1.35 2 H m, 1.46 1 H d (J = 2.5 Hz), 1.1–0.2 2 H m, 0.9 6 H s; mol wt calcd 136, found (MS) m/e 136, 108 (M − H_2CN).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.58; H, 8.82; N, 20.58. Found: C, 70.60; H, 9.03; N, 20.19.

Deuterio-4a: IR (Nujol) 3000, 2240, 1480 cm^{-1}; NMR ($CDCl_3$) δ 2.80 1 H s, 2.33–2.03 2 H m, 1.45–1.00 2 H m, 1.26 3 H s, 1.17 3 H s.

5,5-Dimethyl-2-cyanomethylenepyrrolidine (5a): mp 85–87 °C (ether–petroleum ether); IR (Nujol) 3230, 2180, 1600 cm^{-1}; UV (EtOH) 267 nm (ϵ 23 200); NMR ($CDCl_3$) δ 5.80 1 H bs, 3.85 s and 3.55 s total 1 H, 2.69 2 H m, 1.82 2 H t (J = 7.5 Hz), 1.26 3 H s, 1.24 3 H s; mol wt calcd 136, found (MS) m/e 136, 121 (M − CH_3).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.58; H, 8.82; N, 20.58. Found: C, 70.47; H, 9.10; N, 20.30.

***exo*-6-Cyano-2,2,3-trimethyl-1-azabicyclo[3.1.0]hexane (4b + 4c):** bp 84 °C (0.1 mm); IR (neat) 2250 cm^{-1}; NMR ($CDCl_3$) δ 2.75 1 H m, 2.15 1 H d (J = 2 Hz), 2.58–1.42 3 H m, 1.24–0.86 9 H m; mol wt calcd 150, found (MS) 150.

Anal. Calcd for $C_9H_{14}N_2$: C, 72.00; H, 9.33; N, 18.66. Found: C, 72.20; H, 9.39; N, 18.67.

The two diastereoisomers were separated on a glass column, 6 ft × 0.25 in., 10% Carbowax 20M on 60/80 Diatoport W, column temperature 115 °C, flow 20 mL He/min, in a ratio 48:52. Fraction I was contaminated with fraction II; fraction II was obtained in a pure state. Fraction I: NMR ($CDCl_3$) δ 2.75 1 H m, 2.15 1 H d (J = 2 Hz), 2.58–1.42 3 H m, 1.24 3 H s, 1.20 3 H s, 1.16 3 H s, 1.00 3 H s, 0.90 3 H d (J = 8 Hz), 0.86 3 H d (J = 7 Hz). Fraction II: NMR ($CDCl_3$) δ 2.71 1 H m, 2.58–1.42 3 H m, 2.13 1 H d (J = 2 Hz), 1.16 3 H s, 1.02 3 H s, 0.86 3 H d (J = 7 Hz).

4,5,5-Trimethyl-2-cyanomethylenepyrrolidine (5b): mp 87–89 °C (petroleum ether); IR (Nujol) 3290, 3200, 2190, 1610 cm^{-1}; UV (EtOH) 267 nm (ϵ 20 000); NMR ($CDCl_3$) δ 5.50 1 H bs, 3.85 t (J = 1 Hz), and 3.55 d (J = 1 Hz) total 1 H, 2.85–1.85 3 H m, 1.25 3 H s, 1.04 3 H s, 0.98 3 H d (J = 6 Hz); mol wt calcd 150, found (MS): m/e 150, 135 (M − CH_3), 120 (M − 2CH_3), 105 (M − 3CH_3), 108 (M − CH_3 − HCN).

Anal. Calcd for $C_9H_{14}N_2$: C, 72.00; H, 9.33; N, 18.66. Found: C, 71.87; H, 9.19; N, 18.64.

***exo*-6-Cyano-3,3,5-trimethyl-1-azabicyclo[3.1.0]hexane (4d):** bp 67–68 °C (0.3 mm); IR (neat) 2220 cm^{-1}; NMR ($CDCl_3$) δ 3.10 1 H d (J = 12.75 Hz), 2.46 1 H d (J = 12.75 Hz), 2.20 1 H s, 1.86 2 H m, 1.35 3 H s, 1.01 3 H s, 0.90 3 H s; (C_6D_6) δ 2.86 1 H d (J = 12.75 Hz), 2.05 1 H d (J = 12.75 Hz), 1.60 1 H s, 1.33 2 H m, 1.27 3 H s, 0.78 3 H s, 0.61 3 H s; mol wt calcd 150, found (MS): m/e 150, 135 (M − CH_3).

Anal. Calcd for $C_9H_{14}N_2$: C, 72.00; H, 9.33; N, 18.66. Found: C, 71.50; H, 9.84; N, 18.50.

***exo*-6-Cyano-2,2,4,4-tetramethyl-1-azabicyclo[3.1.0]hexane (4e):** bp 75 °C (0.5 mm); IR (neat) 2250 cm^{-1}; NMR ($CDCl_3$) δ 2.55 1 H d (J = 2.25 Hz), 1.90 1 H d (J = 2.25 Hz), 1.50–1.02 14 H m (includes CH_2 and four methyls at δ 1.31 s, 1.27 s, 1.16 s, 1.12 s); mol wt calcd 164, found (MS) m/e 164, 163, 149 (M − CH_3).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.17; H, 9.75; N, 17.04. Found: C, 73.07; H, 10.03; N, 17.35.

3,3,5,5-Tetramethyl-2-cyanomethylenepyrrolidine (5e): mp 185–187 °C (chloroform–petroleum ether); IR (Nujol) 3270, 2170, 1600 cm^{-1}; UV (CH_3OH) 268 nm (ϵ 18 600); NMR ($CDCl_3$) δ 5.52 1 H bs, 3.45 1 H s, 1.82 2 H s, 1.30 6 H s, 1.21 6 H s; mol wt calcd 164, found (MS) m/e 164, 149 (M − CH_3).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.17; H, 9.75; N, 17.07. Found: C, 73.42; H, 9.85; N, 16.97.

***exo*-6-Carboalkoxy-2,2-dimethyl-1-azabicyclo[3.1.0]hexane. A. 6a, R = Et:** bp 80 °C (0.2 mm); IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.16 2 H q (J = 7.25 Hz), 2.70 1 H m, 2.32–1.90 2 H m, 2.11 1 H d (J = 2.5 Hz), 1.50–1.13 11 H m; mol wt calcd 183, found (MS) 183.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.57; H, 9.29. Found: C, 65.78; H, 9.48.

B. 6a, R = CH_3: oil; IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.66 3 H s, 2.83–2.66 1 H m, 2.13 1 H d (J = 2.5 Hz), 2.30–1.50 2 H m, 1.50–1.17 8 H m; mol wt calcd 169, found (MS) 169.

5,5-Dimethyl-2-carboalkoxymethylenepyrrolidine. A. 7a, R = Et: bp 80 °C (0.1 mm); IR (neat) 3320, 1710, 1600 cm^{-1}; UV (EtOH) 279 nm (ϵ 18 700); NMR ($CDCl_3$) δ 7.70 1 H bs, 4.36 1 H bs, 4.25 2 H q (J = 6.75 Hz), 2.62 2 H t (J = 7.5 Hz), 1.77 2 H t (J = 7.5 Hz), 1.25 3 H t (J = 6.75 Hz), 1.27 6 H s: mol wt calcd 183, found (MS) 183.

B. 7a, R = CH_3: oil; IR (neat) 3320, 1710, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.87 1 H bs, 4.47 1 H s, 3.60 3 H s, 2.70 2 H t (J = 7.5 Hz), 1.80 2 H t (J = 7.5 Hz), 1.27 6 H s; mol wt calcd 169, found (MS) m/e 169, 154 (M − CH_3), 138 (M − OCH_3).

***exo*-6-Carboethoxy-2,2,3-trimethyl-1-azabicyclo[3.1.0]hexane (6b + 6c):** bp 87 °C (0.15 mm); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.97 2 H q (J = 7 Hz), 2.57–2.42 1 H m, 2.19 1 H d (J = 2.25 Hz), 2.13–1.32 3 H m, 1.32–0.67 12 H m; mol wt calcd 197, found (MS) m/e 197, 182 (M − CH_3), 168 (M − C_2H_5).

The two stereoisomers were separated on a glass column, 6 ft × 0.25 in., 10% Carbowax 20M on 60/80 Diatoport W, column temperature 160 °C, flow 40 mL He/min.

4,5,5-Trimethyl-2-carboalkoxymethylenepyrrolidine. A. 7b, R = Et: bp 88 °C (0.2 mm); IR (neat) 3330, 1730 cm^{-1}; UV (CH_3OH) 284 nm (ϵ 10 086); NMR ($CDCl_3$) δ 7.76 1 H bs, 4.34 1 H s, 4.02 2 H q (J = 7 Hz), 2.75–1.44 3 H m, 1.39–0.84 12 H m; mol wt calcd 197, found (MS) m/e 197, 182 (M − CH_3), 152 (M − OC_2H_5).

B. 7b, R = CH_3: oil; IR (neat) 3330, 1730, 1600 cm^{-1}; UV (CH_3OH) 282 nm (ϵ 9103); NMR ($CDCl_3$) δ 7.65 1 H bs, 4.28 1 H s, 3.48 3 H s, 2.85–1.35 3 H m, 1.25–0.75 9 H m; mol wt calcd 183, found (MS) m/e 183, 168 (M − CH_3).

C. 7b, R = *t*-Bu: solid; IR (Nujol) 3330, 1710, 1600 cm^{-1}; UV ($CHCl_3$) 284 nm (ϵ 9546); NMR ($CDCl_3$) δ 7.62 1 H bs, 4.32 1 H s, 2.97–1.57 3 H m, 1.44 9 H s, 1.34–0.67 9 H m; mol wt calcd 225, found (MS) m/e 225, 169 (M − C_4H_8).

***exo*-6-Carboethoxy-2,4,4-trimethyl-1-azabicyclo[3.1.0]hexane (6g + 6h):** oil; IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.35–3.80 2 H q (J = 7.5 Hz), 2.55 1 H d (J = 2.5 Hz), 1.88 1 H d (J = 2.5 Hz), 2.45–1.60 1 H m, 1.55–1.00 14 H m; mol wt calcd 197, found (MS) m/e 197, 182 (M − CH_3), 152 (M − OC_2H_5). This mixture was found to contain two components that could not be separated for determination of their relative amount. Conditions: glass column, 6 ft × 0.25 in., 10% Carbowax 20M on 60/80 Diatoport W, column temperature 160 °C, flow 40 mL He/min.

***exo*-6-Carboalkoxymethyl-2,2,4,4-tetramethyl-1-azabicyclo[3.1.0]hexane. A. 6e, R = Et:** bp 78–79 °C (0.3 mm); IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.25 2 H q (J = 7 Hz), 2.62 1 H d (J = 2 Hz), 2.20 1 H d (J = 2 Hz), 1.58–1.10 17 H m; mol wt calcd 211, found (MS) m/e 211, 196 (M − CH_3).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.24; H, 9.95; N, 6.63. Found: C, 68.58; H, 9.75; N, 6.61.

B. 6e, R = *t*-Bu: oil (purified by preparative gas chromatography); IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.42 1 H d (J = 2.25 Hz), 1.99 1 H d (J = 2.25 Hz), 1.40 9 H s, 1.47–1.07 14 H m; mol wt calcd 239, found (MS): m/e 183 (M − C_4H_8).

Registry No.—**1a**, 3317-61-1; **1b**, 3146-84-7; **1d**, 6931-11-9; **1e**, 10135-38-3; **1f**, 4567-18-4; **2**, 2537-48-6; **3**, 867-13-0; **3** (R = Me), 1067-74-9; **4a**, 57740-50-8; deuterio-**4a**, 61649-96-5; **4b**, 61649-97-6; **4c**, 61740-03-2; **4d**, 61649-98-7; **4e**, 61649-99-8; *E*-**5a**, 57740-52-0; *Z*-**5a**, 57740-51-9; *E*-**5b**, 61650-00-8; *Z*-**5b**, 61650-12-2; **5e**, 61650-01-9; **6a** (R = Et), 57740-49-5; **6a** (R = Me), 61650-02-0; **6b** (R = Et), 61650-03-1; **6c** (R = Et), 61688-35-5; **6e** (R = *t*-Bu), 61650-04-2; **6e** (R = Et), 61650-05-3; **6g**, 61650-06-4; **6h**, 61688-36-6; **7a** (R = Et), 61650-07-5; **7b** (R = Et), 61650-08-6; **7b** (R = Me), 61650-09-7; **7b** (R = *t*-Bu), 61650-10-0; **8**, 61650-11-1.

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(3) E. Breuer, S. Zbaida, J. Pesso, and S. Levi, *Tetrahedron Lett.*, 3104

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(4) Subsequent to submission of our papers to the IUPAC Congress and the Congress of Heterocyclic Chemistry,[2] Black and Davis also reported that reaction of pyrroline 1-oxide derivatives with phosphonates and phosphoranes leads to mixtures of aziridinic and enaminic products: D. St. C. Black and V. C. Davis, *J. Chem. Soc., Chem. Commun.*, 416 (1975).[21]
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(17) All boiling points and melting points are uncorrected. NMR spectra were measured by a JEOL C-60H instrument; all chemical shifts are given in parts per million downfield from Me_4Si. IR spectra were measured on a Perkin-Elmer Model 237 spectrophotometer. UV spectra were measured on a Unicam SP 800A spectrophotometer. Mass spectra were obtained by a Varian MAT CH5 mass spectrometer at 70 eV using a direct inlet system. Microanalyses were carried out by the Hebrew University Microanalytical Laboratory. Gas chromatographic work was carried out on an F and M dual column programmed temperature Model 720 instrument, on an Aerograph Model 90-P-3 equipped with a TC detector and by a Packard Model 7621 gas chromatograph equipped by a flame ionization detector.
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(21) **Note Added in Proof.** While this paper was processed, the full paper by Black and Davis appeared: D. St. C. Black and V. C. Davis, *Aust. J. Chem.*, **29**, 1735 (1976). In this paper full experimental data are given for reactions of Δ^1-pyrroline *N*-oxides **1a**, **1d**, and **1e** with **3** using sodium hydride in DME. The physical data given for the products of the reactions of **1a** and **1e** agree with those obtained in our work for **6a**, **6e**, and **7a** (R = C_2H_5). However, Black and Davis assigned structure **6d** (R = C_2H_5) for the product of the reaction of **1d** with **3**. In this reaction we obtained a mixture of products **6g** and **6h**.

Cycloaddition Reactions of Vinyl Sulfene Generated from Thiete 1,1-Dioxide[1]

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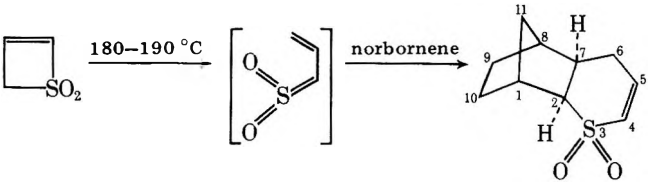
Thermolysis of thiete 1,1-dioxides in the presence of norbornenes gives cycloadducts of the Diels–Alder type resulting from the trapping of vinyl sulfene formed by ring opening of the thiete 1,1-dioxides. Other cyclic or acyclic alkenes gave little or no reaction.

Sulfenes ($R_2C{=}SO_2$) undergo [2 + 2] cycloadditions to activated olefins (e.g., enamines) to yield thietane 1,1-dioxides,[2] and sulfene itself ($CH_2{=}SO_2$) may serve as a dienophile in a [4 + 2] cycloaddition to enamino ketones.[3] Vinyl sulfenes (e.g., $R_2C{=}CHCH{=}SO_2$) have the capability of undergoing both [2 + 2] and [4 + 2] cycloadditions in which the vinyl sulfene may serve as either the two- or the four-electron reactant. These conjugated sulfenes have been proposed as intermediates in reactions of 1- or 2-propenesulfonyl chloride,[4] in the photolysis of cyclic unsaturated sultones and sulfones,[5] and in the thermal decomposition of thiete 1,1-dioxides.[6] The presence of vinyl sulfene intermediates has been supported by trapping experiments with phenol[6b,d] and by the formation of sultines[6a–d,g] and α,β-unsaturated carbonyl compounds.[6c,e,f] This report is about the trapping of vinyl sulfene intermediates acting as dienes in Diels–Alder or [4 + 2] cycloaddition reactions. Previously, Truce and Norell reported that vinyl sulfene obtained from 1- or 2-propenesulfonyl chloride gave a low yield (6.5–7.6%) of a [4 + 2] adduct with ketene diethyl acetal.[4a]

Results and Discussion

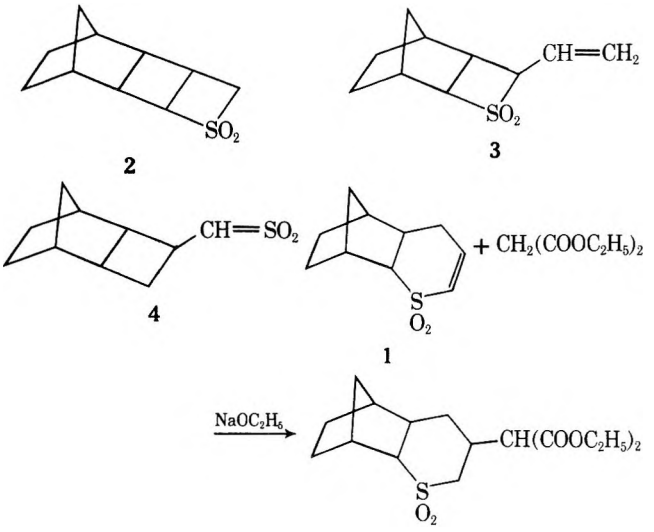
When thiete 1,1-dioxide is thermolyzed at 180–190 °C in the presence of norbornene in a sealed, degassed flask for 5 days, a 63–79% yield of an adduct, **1**, was obtained. The solvent was either *m*-xylene or benzene, the latter being preferred because of higher yields and the ease of workup of the reaction mixture. The thermolysis is quite clean, no tar being formed. At the end of the reaction period, a pale yellow solution remains which yields a crystalline adduct on removal of solvent.



1

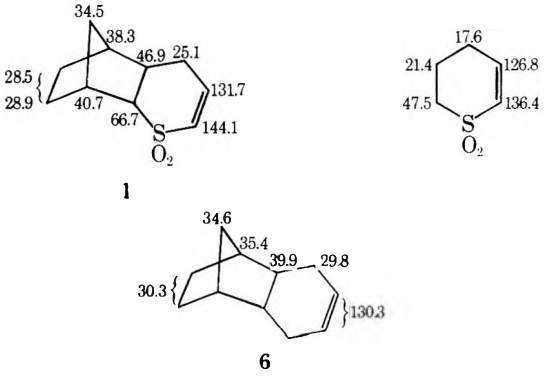
The elemental analysis and mass spectrum are in agreement with the proposed structure, **1**, 3-thiatricyclo[6.2.1.$0^{2,7}$]undec-4-ene 3,3-dioxide. In addition to providing the molecular weight, the mass spectrum shows evidence for the retro-Diels–Alder reaction: intense ions at *m/e* 94 for norbornene and at *m/e* 104 for vinyl sulfene are observed. The presence of the sulfone group is indicated by strong absorption in the infrared at 1298 and 1120 cm^{-1}. A carbon–carbon double bond is indicated by the infrared spectrum (1620 cm^{-1})[7] and by the ^1H and ^{13}C NMR spectra.[8] The presence of the double bond excludes structure **2** and the ^1H NMR spectrum excludes structures **3** and **4**; the latter, a sulfene, would not be expected to be particularly stable. The double bond in **1** is conjugated with the sulfone group and undergoes, as expected, a Michael reaction with the anion of diethyl malonate to yield **5**.

The carbon chemical shifts of **1** are compared in Chart I with those of dihydrothiapyran 1,1-dioxide and with those calculated[9] for the strictly carbocyclic analogue (**6**) of **1**. The chemical shifts of the alkene carbons in **1** are assigned on the basis of the shifts observed in thiete 1,1-dioxide.[10] A partially proton-decoupled ^{13}C NMR spectrum of **1** shows a doublet for each alkene carbon atom which is caused by a one-bond coupling ($J_{\alpha CH}$ = 165; $J_{\beta CH}$ = 184 Hz). Each component of the



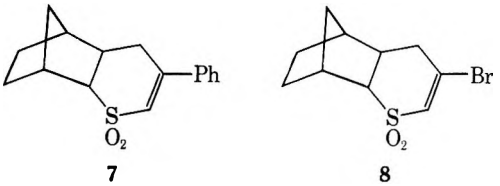
two doublets is split further into an apparent triplet (probably consisting of overlapping doublets) by long-range couplings involving the alkene protons and the methylene protons α to the double bond ($J \sim 6$ Hz). The spectrum was obtained on a Varian CFT-20 spectrometer with the decoupler on during pulse delay and off during acquisition: 4K data points, 20 000 transients, 3-μs pulse width, 0 pulse delay, 0.5-s acquisition time. The partial proton decoupling also aided in distinguishing methine and methylene carbons in **1**. The near identity of the chemical shifts for C-9 and C-10 (δ 28.5, 28.9) in adduct **1** and the similarity of the shifts to those for C-2 and C-3 in norbornane (δ 30.1)[11] support a cis-exo configuration for **1**. Endo-2-substituted norbornanes show significant shifts to higher field for C-6 (δ C-6, exo 2-CH_3, 29.0; endo 2-CH_3, 22.4; exo 2-$COOCH_3$, 28.7; endo 2-$COOCH_3$, 25.1).[11] A trans configuration of the fused six-membered sulfone ring obviously would require one endo and one exo linkage and C-9 and C-10 should differ considerably in their chemical shifts.

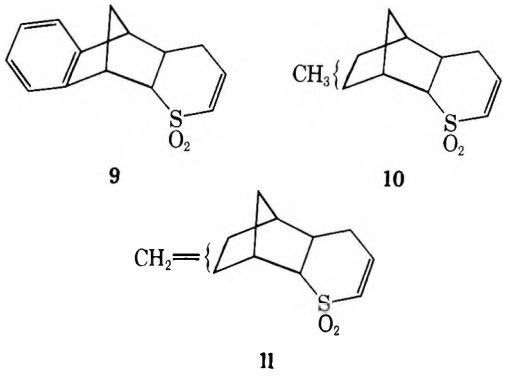
Chart I. Carbon Chemical Shifts (δ) Relative to Me_4Si for 1 and Related Compounds[a]



[a] The shifts for **6** are calculated ones.[9]

Adducts **7–11** also were obtained from 3-phenylthiete 1,1-dioxide (60–71%) or 3-bromothiete 1,1-dioxide (52%) and norbornene and from thiete 1,1-dioxide and benzonorbornene (48–60%), 2-methylnorbornene (55–73%), and 2-methylene-

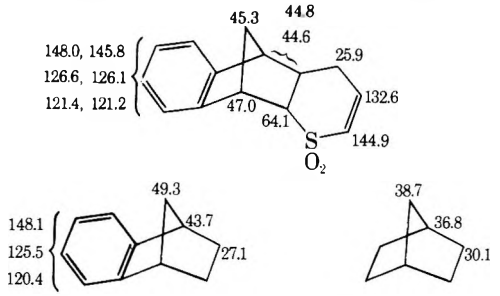




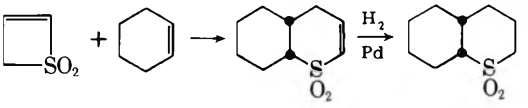
norbornene (50%). The regiospecificity of addition to the latter two norbornenes is not known.

The carbon chemical shifts of the benzonorbornene adduct are compared with those of benzonorbornene[12] itself, and with norbornane,[11] in Chart II. The assignment of the shift of δ 25.1 to the allylic carbon (C-6) in **1** is supported by the spectrum of **9** in which absorption for the allylic carbon is at δ 25.9.

Chart II. Carbon Chemical Shifts (δ) Relative to Me_4Si

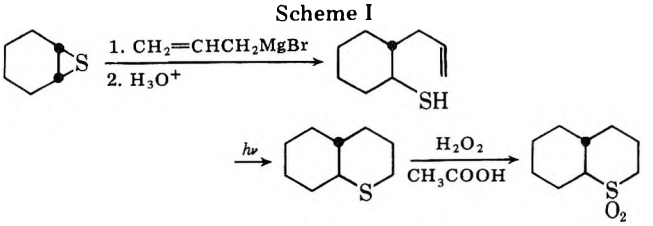


Thermolysis of thiete 1,1-dioxide in cyclohexene for 5 days at 170 °C gave mainly tar and a very low yield (0.6%) of an adduct, formulated as **12**. Attempts to improve the yield of adduct failed and in most cases no adduct at all was obtained. Only the elemental analysis, infrared, and mass spectra could be obtained on the small quantity of **12** available; these data,



however, were in agreement with the proposed structure. Both cyclohexene (*m/e* 82) and vinyl sulfene (*m/e* 104) fragments are observed in the mass spectrum. The cis thiadecalin structure is suggested by analogy with other cis Diels–Alder adducts. Hydrogenation of the double bond in **12** yields a saturated sulfone, **13**, mp 75–77 °C, whose infrared spectrum and mass spectrum are similar to those obtained for the saturated sulfone (mp 109–110 °C) obtained from 1-thiadecalin[13] as outlined in Scheme I. The thiadecalin synthesis ought to

Scheme I



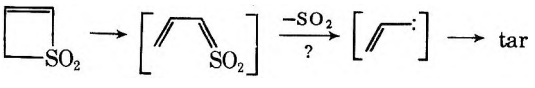
result in a trans ring fusion. Unfortunately, not enough of **13** could be obtained for a thorough investigation of its stereochemistry.

The failure of cyclohexene to give an appreciable yield of adduct points to the strain energy associated with the double

bond in the norbornenes as the origin of the facile reaction with vinyl sulfene. The difference in strain energy between norbornane and norbornene is calculated to be about 9 times greater than the difference between cyclohexane and cyclohexene.[14] Norbornene functions as a dienophile in Diels–Alder cycloadditions and reacts about 24 times faster with hexachlorocyclopentadiene than cyclohexene does.[15a] If vinyl sulfene were a highly reactive diene component in a Diels–Alder reaction, it should be less discriminating toward various alkenes than hexachlorocyclopentadiene and considerable addition of vinyl sulfene to cyclohexene would be expected.[15b] Therefore, the data available suggest that vinyl sulfene is not necessarily a particularly reactive dienelike species.

Thermolysis of thiete 1,1-dioxide with camphene, bicyclo[2.2.2]octene, *cis*-2-butene, cyclopentene, dicyclopentadiene, and diphenylacetylene yielded only tar.

After the first synthesis of thiete 1,1-dioxide,[16] we observed that it decomposed considerably above its melting point to a black tar with the evolution of what appeared to be sulfur dioxide as indicated by its odor and acidic properties (pH paper). The possible dissociation of vinyl sulfene to vinyl carbene and sulfur dioxide was considered, and it was an attempt to trap the vinyl carbene that led us to do the thermolysis reaction in cyclohexene. Although the dissociation of sulfene ($CH_2{=}SO_2$), itself to methylene and sulfur dioxide is believed to be highly endothermic,[17] the loss of sulfur dioxide from vinyl sulfene may be more favorable because of the possibilities for conjugative stabilization in vinyl carbene as compared to methylene. The tar, in part, may be derived from products arising via vinyl carbene whose reactions and electronic structures may be diverse.[18] Tar formation occurs in 36–48 h on heating thiete 1,1-dioxide alone in benzene at 170 °C. The decomposition occurs within 10 min at 260 °C in benzene; at this temperature in the presence of norbornene only a 20% yield of 1 is obtained along with tar. This suggests that at lower temperatures in solution the decomposition of vinyl sulfene is slow relative to its addition to norbornene; at higher temperatures the decomposition competes more favorably with the cycloaddition. The lack of any observed addition products of vinyl carbene with the alkenes may be caused by instability of the adducts, e.g., vinylcyclopropanes. However, one mode of decomposition of the latter is to cyclopentene derivatives,[19] none of which were observed. Neither were any adducts of vinyl sulfene and cyclopropene found.



Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 137 infrared spectrophotometer. The proton magnetic resonance spectra were taken on either Varian A-60, T-60, or XL-100 spectrometers. The carbon-13 nuclear magnetic resonance spectra were obtained on Varian XL-100, CFT-20, and JEOL FX-60 spectrometers. The ^{13}C NMR absorptions were referenced to tetramethylsilane. Microanalyses were performed at Micro-Analysis Inc., Wilmington, Del. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6E single focusing spectrometer. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected.

The thermolysis reactions of thiete 1,1-dioxides were run in round-bottomed flasks with a break seal and a side arm. The flasks and their contents were degassed under vacuum by cooling in liquid nitrogen followed by gradual warming to room temperature. This was repeated until gases were no longer seen to issue from the flask. The flasks with their contents were sealed under vacuum and heated in an oil bath.

Thermolysis of Thiete 1,1-Dioxide. A. With Norbornene. Thiete 1,1-dioxide[16] (1.04 g, 10 mmol), norbornene (1.41 g, 15 mmol), and dry benzene (15 mL, distilled and stored over Linde 4A molecular sieves) were placed in the thermolysis flask. The flask and its contents were degassed four times and heated at 180–190 °C for 5 days. The flask was cooled and opened, and the solvent was removed from the pale yellow solution at reduced pressure, leaving an oil which rapidly crystallized. Recrystallization from ether containing a few drops of ethanol gave adduct **1** (3-thiatricyclo[6.2.1.$0^{2,7}$]undec-4-ene 3,3-dioxide) as colorless needles (1.5 g, 7.6 mmol, 79%): mp 109–110 °C; IR (KBr) 1620 (m), 1298 (s), 1120 (s), 870 (s), 790 (s), and 680 cm^{-1} (s); ^1H NMR (60 MHz, $CDCl_3$) δ 6.8 (triplet of doublets, 1 H), 6.5 (doublet of doublets, 1 H), 2.9 (m, 2 H), 2.3 (m, 5 H), 1.7 (m, 2 H), 1.2 (m, 3 H); ^{13}C NMR δ 25.1 (t), 28.5 (t), 28.9 (t), 34.5 (t), 38.3 (d), 40.7 (d), 46.9 (d), 66.7 (d), 131.7 (d), 144.1 (d); mass spectrum (70 eV) *m/e* 198 (M), 150 (M − SO), 134 (M − SO_2), 133 (M − SO_2H), 104, 94. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.61; H, 7.07; S, 16.16. Found: C, 60.42; H, 6.99; S, 16.10.

Diethyl malonate (1.6 g, 10 mmol) was added to a stirred solution of sodium ethoxide [prepared by adding sodium (0.23 g, 10 mmol) to absolute ethanol (25 mL)]. The resulting solution was stirred for 5 min, and then adduct **1** (1.98 g, 10 mmol) was added in portions during 5 min. The solution was stirred at reflux for 3 h, cooled, and acidified with acetic acid (10%, 15 mL). The aqueous solution was extracted continuously with methylene chloride (100 mL) for 12 h. The methylene chloride was washed with sodium bicarbonate (10 mL, 10% solution), dried ($MgSO_4$), and filtered, and the solvent removed to give a brown oil that slowly crystallized at 0 °C. Recrystallization from ether gave the Michael adduct, **5**, as colorless crystals (2.7 g, 7.5 mmol, 75%): mp 78–80 °C; IR (KBr) 2950 (m), 1740 (s), 1298 (s), 1120 (s), 1020 (m), and 860 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 4.2 (q, 4 H, J = 6 Hz), 2.6–3.6 (m, 6 H), 2.0 (m, 10 H), 1.2 (t, 6 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 25.4, 28.1, 28.9, 31.4, 33.8, 36.5, 41.2, 43.9, 49.3, 56.6, 61.1, 61.2, 63.3, 166.9, 167.5. Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.98; H, 7.26; S, 8.94. Found: C, 56.74; H, 7.15; S, 9.02.

B. With Benzonorbornadiene. Thiete 1,1-dioxide (250 mg, 2.4 mmol), benzonorbornadiene[20] (430 mg, 3.0 mmol), and benzene (10 mL) were treated as described for the reaction of thiete 1,1-dioxide and norbornene. The flask and its contents were heated at 160–170 °C for 5 days. A light yellow solid was obtained which was recrystallized from benzene containing a few milliliters of ether to give colorless crystals of **9** (340 mg, 1.37 mmol, 60%): mp 186–187 °C; IR (KBr) 3050 (w), 1620 (m), 1300 (s), 1100 (s), 890 (m), 850 (m), 790 (m), 760 (s), and 750 cm^{-1} (s); ^1H NMR (Me_2SO-d_6) δ 6.6 (m, 5 H), 6.2 (doublet of doublet, 1 H), 3.6 (m, 1 H), 1.6–3.2 (m, 7 H); ^{13}C NMR (Me_2SO-d_6) δ 25.9, 44.6, 44.8, 45.3, 47.0, 64.1, 121.2, 121.4, 126.1, 126.6, 132.6, 144.9, 145.8, 148.0; mass spectrum (70 eV) *m/e* 246 (M), 198 (M − SO), 182 (M − SO_2), 181 (M − SO_2H), 142, 104. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.2; H, 5.69; S, 13.0. Found: C, 68.4; H, 5.53; S, 13.04.

C. With 5-Methylene-2-norbornene. Thiete 1,1-dioxide (1.04 g, 10 mmol) and 5-methylene-2-norbornene (Aldrich Chemical Co.) (1.1 g, 11 mmol) in *m*-xylene (10 mL) were heated at 180–190 °C for 5 days to give an oil that was chromatographed on Florisil (elution with ether) to give a white, fluffy solid, **11** (1.05 g, 5 mmol, 50%): mp 75–77 °C; IR (thin film) 3000 (m), 1670 (m), 1620 (m), 1300 (s), 1120 (s), 880 (m), and 805 cm^{-1} (m); NMR ($CDCl_3$) δ 6.8 (triplet of doublets, 1 H), 6.4 (doublet of doublets, 1 H), 4.9 (d, 2 H), 3.2 (m, 2 H), 1.0–2.8 (m, 8 H); mass spectrum (70 eV) *m/e* 210 (M), 162 (M − SO), 146 (M − SO_2), 145 (M − SO_2H), 106, 104. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.86; H, 6.67; S, 15.24. Found: C, 62.78; H, 6.76; S, 14.92.

D. With 5-Methyl-2-norbornene. Thiete 1,1-dioxide (2.00 g, 19.2 mmol), 5-methyl-2-norbornene (Aldrich Chemical Co.) (4.54 g, 38.4 mmol), and benzene (20 mL) were heated at 140–145 °C for 4 days to give an oil which crystallized rapidly. The product was recrystallized from acetone–heptane (20 mL, 90:10, 0–5 °C) to give white crystals of **10** (2.97 g, 14.0 mmol, 73%): mp 83–84 °C; IR (KBr) 1640 (m), 1298 (s), 1260 (s), 1120 (s), 870 (m), and 805 cm^{-1} (m); NMR (100 MHz, $CDCl_3$) δ 6.8 (triplet of doublets, 1 H), 6.5 (doublet of triplets, 1 H), 2.8 (m, 2 H), 1.2–2.5 (m, 9 H), 1.0 (d, 3 H); mass spectrum (70 eV) *m/e* 212 (M), 165 (M − SO), 149 (M − SO_2), 148 (M − SO_2H), 109, 104. Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.22; H, 7.60; S, 15.10. Found: C, 62.15; H, 7.19; S, 14.83.

E. With Cyclohexene. Thiete 1,1-dioxide (1.04 g, 10 mmol) and cyclohexene (10 mL) were heated at 160–170 °C for 5 days to give a black, tarry mixture. After the excess cyclohexene was removed the residue was extracted with methylene chloride (3 × 5 mL) and subjected to column chromatography (silica gel, elution by 1:1 ether–ethanol). A white, crystalline material tentatively identified as **12** was obtained (11 mg, 0.060 mmol, 0.6%): mp 102–103 °C; IR (KBr) 2950 (m), 1640 (m), 1460 (m), 1298 (s), 1120 (s), and 870 cm^{-1} (m); mass spectrum (70 eV) *m/e* 186 (M), 122 (M − SO_2), 121 (M − SO_2H), 104, 82. Anal. Calcd for $C_9H_{14}O_2S$: C, 58.11; H, 7.52. Found: C, 57.92; H, 7.43.

Compound **12** (15.8 mg, 0.085 mmol) in ethanol was reduced in a

Brown microhydrogenator with a palladium/carbon catalyst to yield a white, crystalline material tentatively identified as the saturated sulfone **13** (15 mg, 0.080 mmol, 94%): mp 75–77 °C; IR (KBr) 2950 (m), 1450 (m), 1298 (s), 1120 (s), and 870 cm^{-1} (m); mass spectrum (70 eV) *m/e* 188 (M), 124 (M − SO_2), 123 (M − SO_2H).

1-Thiadecalin 1,1-Dioxide. 1-Thiadecalin[13] (1.0 g, 0.64 mmol) was dissolved in glacial acetic acid (2 mL). Excess hydrogen peroxide (30%) was added and the mixture was allowed to stand overnight. Dilution with water (10 mL) gave a precipitate which was removed by filtration, dried, and sublimed to give a white, crystalline material (654 mg, 0.34 mmol, 55%): mp 109–111 °C (lit.[13] mp 114–114.9 °C); IR (KBr) 2950 (m), 1450 (m), 1298 (s), 1120 (s), 875 (m), and 720 cm^{-1} (m); NMR ($CDCl_3$) δ 2.8–3.2 (m, 2 H), 2.4–2.75 (m, 1 H), 0.8–2.3 (m, 13 H); mass spectrum (70 eV) m/e 188 (M), 124 (M − SO_2), 123 (M − SO_2H). Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.56; S, 17.0. Found: C, 57.34; H, 8.51; S, 16.78.

Thermolysis of 3-Phenylthiete 1,1-Dioxide with Norbornene. 3-Phenylthiete 1,1-dioxide[21] (450 mg, 2.5 mmol), norbornene (350 mg, 3.1 mmol), and *m*-xylene (10 mL, distilled and stored over Linde 4A molecular sieves) were heated at 190–200 °C for 5 days. A light tan solid was obtained which was recrystallized from benzene containing a few drops of ether to give adduct **7** as colorless crystals (412 mg, 1.5 mmol, 60%): mp 89–91 °C; IR (KBr) 3050 (m), 1610 (m), 1298 (s), 1120 (s), 875 (s), 840 (s), and 745 cm^{-1} (s); NMR (60 MHz, $CDCl_3$) δ 7.35 (broad singlet, 5 H), 6.5 (s, 1 H), 1.8–3.2 (complex multiplet, 7 H), 1.4 (m, 5 H); mass spectrum (70 eV) *m/e* 274 (M), 226 (M − SO), 210 (M − SO_2), 209 (M − SO_2H), 172, 104. Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.56, 11.68. Found: C, 69.96; H, 6.45; S, 11.91.

Thermolysis of 3-Bromothiete 1,1-Dioxide with Norbornene. 3-Bromothiete 1,1-dioxide[21] (250 mg, 1.4 mmol), norbornene (188 mg, 3 mmol), and *m*-xylene (10 mL) were heated at 160–170 °C for 7 days, giving an oil that crystallized upon the addition of pentane (10 mL) and cooling to −20 °C. The crude product was purified by chromatography on a short column of Florisil (ether) to give a white, granular solid, **8** (200 mg, 0.73 mmol, 52%): mp 106–107 °C; IR (KBr) 1600 (m), 1300 (s), 1120 (s), 1000 (m), 865 (m), and 800 cm^{-1} (m); NMR (60 MHz, $CDCl_3$) δ 6.8 (s, 1 H), 2.8 (m, 5 H), 1.0–2.3 (m, 7 H); mass spectrum (70 eV) *m/e* 277 (M), 229 (M − SO), 213 (M − SO_2), 212 (M − SO_2H), 175, 104. Anal. Calcd for $C_{10}H_{13}BrO_2S$: C, 43.33; H, 4.72; Br, 28.83. Found: C, 43.51; H, 4.80; Br, 28.67.

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Registry No.—**1**, 61770-37-4; **5**, 61770-38-5; **7**, 61770-39-6; **8**, 61770-40-9; **9**, 61770-41-0; **10**, 61787-31-3; **11**, 61787-32-4; **12**, 61770-42-1; **13**, 61770-43-2; thiete 1,1-dioxide, 7285-32-7; norbornene, 498-66-8; diethyl malonate, 105-53-3; benzonorbornadiene, 4453-90-1; 5-methylene-2-norbornene, 694-91-7; 5-methyl-2-norbornene, 882-96-8; cyclohexene, 110-83-8; 1-thiadecalin 1,1-dioxide, 29108-28-9; 1-thiadecalin, 29100-30-9; hydrogen peroxide, 7722-84-1; 3-phenylthiete 1,1-dioxide, 25903-17-7; 3-bromothiete 1,1-dioxide, 59463-74-0.

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(21) Kindly supplied by Dr. Thomas R. Nelsen.

A Sterically Efficient Synthesis of (Z)-5-Fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic Acid and Its S-Oxide,[1,2] Sulindac[1]

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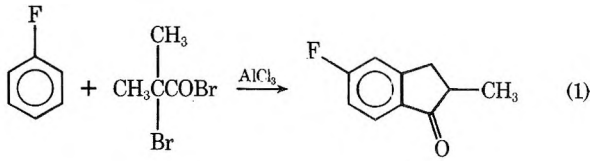
Synthesis of (Z)-5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid (12) via its Z diene tautomer (10) was carried out virtually free of interference from the corresponding E isomers (11 and 13). The sequence may have general application to synthesis of a wide variety of 1,2,3-trisubstituted indenes. The synthesis proceeds from fluorobenzene to 5-fluoro-2-methyl-1-indanone (1) by a Friedel–Crafts acylation–cyclization. Preparation in good yield of p-methylthiobenzylmagnesium chloride (3) for reaction with 1 was dependent on solvent polarity and on excess of magnesium, and dehydration of the resulting carbinol (5) afforded product with an endocyclic double bond, indene 6. Elaboration of the acetic acid side chain was effected with glyoxylic acid and tetraalkylammonium hydroxides which are uniquely suited as catalysts compared to alkali hydroxides. This condensation was studied and a rationale for the role of R_4NOH based on solubility and steric bulk is presented. Successful condensation afforded (Z)-6-fluoro-2-methyl-3-(p-methylthiobenzyl)-1-indenylideneacetic acid (10) which was efficiently isomerized with concentrated HCl/CH_3CO_2H to 12 (>90% yield). From 10 and 12 the corresponding sulfoxides 14 and 15 were prepared, and tautomerization of 14 was studied briefly.

Results and Discussion

Since disclosure of the synthesis of indene isosteres of indomethacin,[3] the assignment for the most stable double bond configuration at C-1 for one of these isosteres, (Z)-1-(p-chlorobenzylidene)-5-methoxy-2-methyl-3-indenylacetic acid,[4] was confirmed by x-ray and NMR data.[5] We now wish to report a sterically efficient synthesis of one (12) of this family of 1-benzylidene 3-indenylacetic acids and its S-oxide (15) by preparation and isomerization of a diene tautomer (10). The sequence discussed contains several points of interest and should be of use as a facile, general synthesis of 1,2,3-trisubstituted indenes constructed from a variety of benzene derivatives or indanones.

Entry to 10 is conveniently provided by preparation and reaction of the appropriate indanone with a benzyl Grignard reagent, dehydration of the carbinol, and condensation of glyoxlic acid with the resulting indene.

Thus, fluorobenzene reacted with α-bromoisobutyryl bromide in the presence of $AlCl_3$ to give 5-fluoro-2-methyl-1-indanone (1) directly,[6] eq 1.



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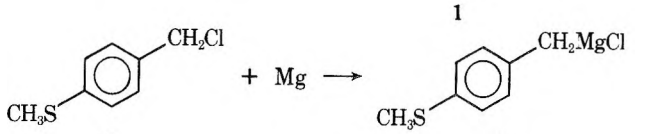

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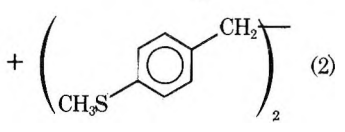


(2)

4

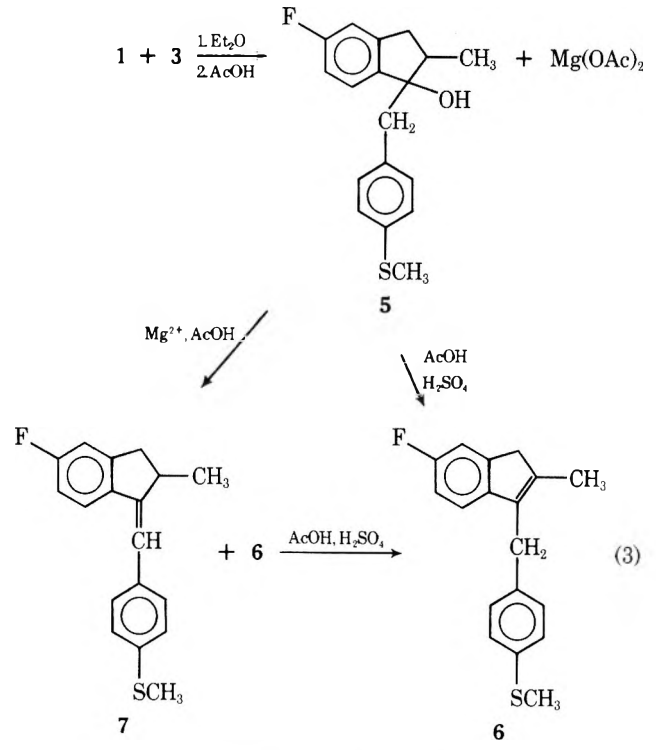
Preparation of p-methylthiobenzylmagnesium chloride (3) for reaction with 1 required an excess of magnesium to suppress competitive coupling which leads instead to 1,2-bis(p-methylthiophenyl)ethane (4), eq 2. Ether was also shown to be crucial to successful formation of 3. Formation of 3 in diminishing volumes of ether produced a discernible drop in the yield of 3 as summarized in Figure 1.

Substitution of THF for ether led to a large quantity (42%) of 4 and lower yield (26.6%) of 3 as did increasing substitution of benzene or toluene, also in place of ether. On one hand the higher polarity of THF probably promotes coupling by direct displacement of chloride, and on the other hand dilution of ether with benzene (or toluene) undoubtedly interferes with solvation of the organomagnesium halide with a corresponding increase in its nucleophilicity toward p-methylthiobenzyl chloride. A similar rate-accelerating effect of THF on coupling reactions of aryllithiums with alkyl halides has also been noted.[7]

Addition of 1 to an ethereal solution of 3 is characterized by a transient (1–2 s), highly localized, blood-red color where the reagents contact each other. The decreasing intensity of this color and its eventual absence was used to determine complete conversion of the Grignard reagent and generally agreed quite well with the titration method given in the Experimental Section. Addition of 1 past this point (ca. 0.85 mol of 1) gave no increase in yield of products 5 or 6.

Although carbinol 5 could be isolated, it was more convenient to quench directly and to dehydrate the Grignard mixture with a solution of acetic and sulfuric acids to obtain product with an endocyclic double bond, 6-fluoro-2-methyl-3-(p-methylthiobenzyl)indene (6), eq 3. If quenched into acetic acid only, the mixture contained an additional product with an R_f by TLC slightly faster than 6. This was isolated by preparative GLC and by independent synthesis as the exocyclic isomer, 7, an indan arising from dehydration catalyzed by Mg^{2+}. By TLC, solutions containing 7 were converted wholly to 6 with H_2SO_4 in acetic acid, but no dehydration or prototropic shift occurred in acetic acid alone.

Two-carbon homologation by condensation of glyoxylic acid or its esters with a variety of acidic methylene compounds is recorded. Representative of these are α-tetralones,[8] ethyl acetoacetate,[9] and acetophenones.[10,11] Also, formation of indenyl anion is reported to occur readily and the anion to undergo oxidation,[12] alkylation,[13] prototropism,[13b,14] condensation,[12a,13b,15] and carboxylation.[16] In no instance, however, were we similarly able to obtain measurable reaction of 6 with glyoxylic acid to afford 8 either with alkali hydroxides or alkoxides, ordinary tertiary organic amines, or heat.



Indeed, all attempts to obtain useful solubility of sodium or potassium glyoxylate in nonaqueous systems failed, and in water the Cannizzaro reaction of glyoxylic acid with NaOH or KOH was shown to proceed quite rapidly at 37 °C in a ^{1}H NMR probe. Both difficulties, solubility and the Cannizzaro reaction, were circumvented by use of tetraalkylammonium hydroxides (Triton B or Me_4NOH) in stoichiometric quantities. This afforded not only solubility for glyoxylate ion but permitted only very slow conversion via the Cannizzaro reaction. Figure 2 compares the relative effect of three caustic bases (NaOH, KOH, Triton B) on conversion of glyoxylate to glycolate and oxalate ions. The striking difference of 100:10:1 in relative rates as shown in Figure 2 is attributed to increasing size of the cation. The generally accepted mechanism[17,18] for the Cannizzaro reaction requires formation of a termolecular complex comprised of 2 mol of an aldehyde and 1 mol of the base, each properly aligned for concerted reaction; but a tetralkylammonium cation quite likely is too bulky to be comfortably accommodated in such a complex. The effect of cationic size and charge number on the rate of the Cannizzaro reaction of formaldehyde is known but no difference between sodium and potassium was reported.[17] In similar fashion the steric bulk of triethylbenzylammonium ion was recently invoked to account for the slower Cannizzaro reaction of benzaldehyde in favor of its condensation with dimethyl sulfone.[19]

Thus, use of Triton B to effect condensation and dehydration between **6** and glyoxylic acid led to isolation of (*Z*)-6-fluoro-2-methyl-3-(*p*-methylthiobenzyl)-1-indenylideneacetic acid (**10**) in 75% yield. Indene also reacted under identical conditions to give (*Z*)-1-indenylideneacetic acid. Evidence for the *Z* configuration about the exocyclic double bond as shown for **10** (eq 4) was obtained when irradiation of the C_2 CH_3 group during ^{1}H NMR produced a nuclear Overhauser enhancement measured as 49% for the vinylic side-chain proton α to $-CO_2H$. Examination by ^{1}H NMR of crystallization liquors from **10** provided evidence of only a few percent of the *E* isomer (**11**), the preponderant material being **10**. Isomer **11** was crystallized from mother liquors and characterized. 1-Indenylideneacetic acid was assigned the *Z* configuration because the upfield position (δ 6.75) of the side-chain proton was similar to that (δ 6.5) for **10**.

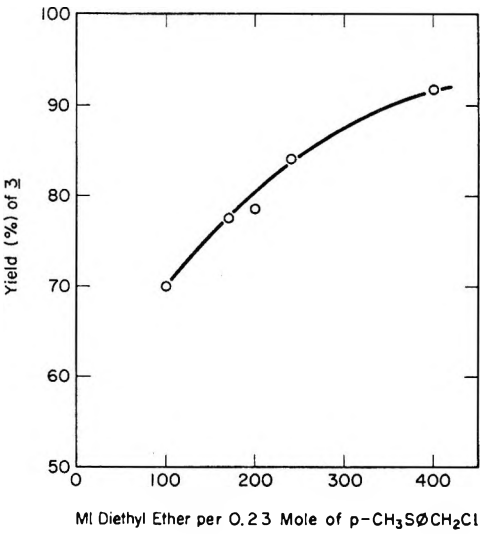
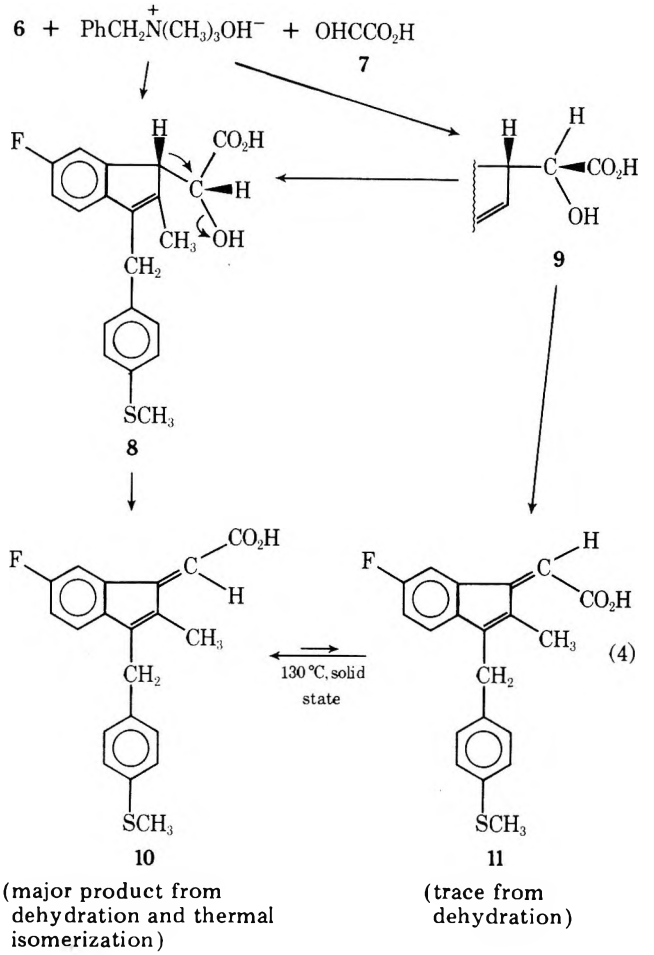


Figure 1. Yield of *p*-methylthiobenzylmagnesium chloride (**3**) vs. mL of ether. Assayed by direct titration with 2-butanol and 2,2′-biquinoline. See Experimental Section.



(major product from dehydration and thermal isomerization)

(trace from dehydration)

The high preference for **10** suggests that base-catalyzed dehydration occurs rapidly on only one of the two possible enantiomeric pairs of carbinols. Two of the diastereomers are shown in eq 4 as **8** and **9**. If dehydration occurs by E2 elimination of hydroxide then **10** would be expected from **8** rather than from **9**. At the same time there is evidence that **9** is converted to **8** either by epimerization at the α carbon or by a retrograde reaction to starting materials followed by recondensation. Indeed, two carbinols are observed by TLC and one disappears much more rapidly, but not completely until the overall reaction is done. The phenomenon was also observed

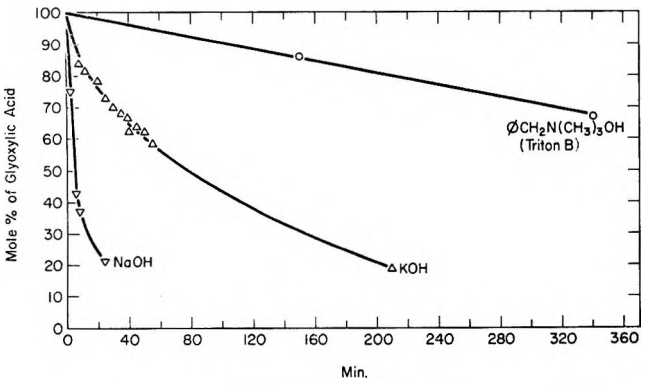


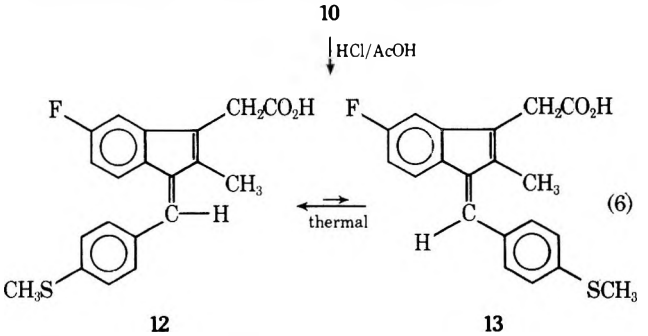
Figure 2. Effect of 4 equiv each of three caustic bases on conversion of glyoxylic acid in D_2O (35 °C) to oxalic and glycolic acids as measured by ^1H NMR. Relative rates at 67 mol % remaining (33% conversion), NaOH:KOH:Triton B = 100:10:1.

by crystallization of a carbinol believed to be **9**, followed by its dehydration to **10** with Triton B. During dehydration of pure **9** a second material (8?) slightly less polar by TLC again rapidly formed and persisted after disappearance of **9**. That **11** arises from **9** was demonstrated by treating pure **10** with methanolic Triton B and observing no trace of isomerization at 50 °C, the usual reaction temperature. Carbinol **9** was formed from **6** and glyoxylic acid with no dehydration under catalysis by 1,1,3,3-tetramethylguanidine in DMF, whereas triethylamine and pyridine failed (eq 5). Only with OH^-

$$6 + OHCCO_2H + (CH_3)_2NC(=NH)N(CH_3)_2 \longrightarrow 9 \not\rightarrow 10 \quad (5)$$

(Triton B or Me_4NOH) was **10** formed. Mineral acids were without dehydrative effect on **8** and **9**.

Tautomerism of **10** with HCl proved facile and highly productive of the single isomeric product **12**. Heating an orange-colored slurry of **10** in a solution of hydrochloric acid in acetic acid (95 °C, 10 h) afforded a yellow slurry of **12** in 85% yield. Inspection by ^1H NMR of the filtrate solids revealed only about 2% each of **10** and of **13**, the *E* isomer of **12**. We know of no similarly specific diene tautomerism used for preparative purposes. An authentic sample of **13** was obtained by fractional crystallization from mother liquors of **12**.



(6)

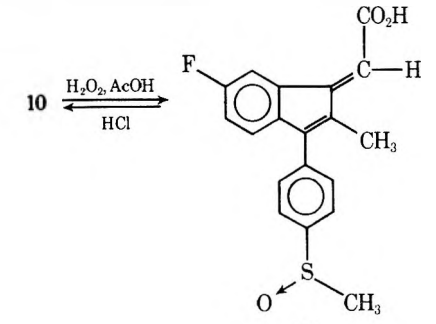
12 (major product from 10 and thermal isomerization) **13**

An attempt to discern the site(s) of protonation and/or of addition of HCl to **10** was wholly unsuccessful in a sealed NMR tube with CD_2ClCD_2Cl saturated with HCl. Heating the sealed probe at 100 °C gave slow tautomerization, but no new proton resonances or intermediates were observed.

The superiority of hydrogen chloride over a caustic base for diene isomerization is amply demonstrated by the equilibrium mixture of products observed by ^1H NMR. One mole of **10** and 2 mol of Triton B in pyridine gives 72% of **12**, 9% of **13**, and 19% of starting material **10**.

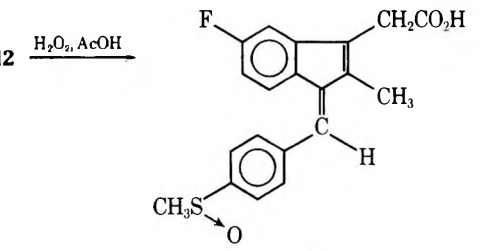
Thermal $Z \rightleftarrows E$ isomerization was studied briefly, both in solution and in the crystalline state. Either **12** or **13** could be converted to an equilibrium mixture of 82:18 (**12**/**13**) as measured by ^1H NMR. At 110 °C the half-lives are 45 min in pyridine-d_5 and 20 min in Me_2SO-d_6. At 135 °C crystalline **13** was converted largely to **12**, whereas **12** was virtually unchanged when heated in the solid state. Similarly, **11** at 130 °C afforded mostly **10** by TLC. In no instance was thermally induced diene tautomerism observed between **10** and **12**.

Oxidation of **10** and **12** to the corresponding sulfoxides **14** and **15** was facile and straightforward with hydrogen peroxide in the presence of acetic acid. Attempted tautomerization of **14** to **15** by HCl was accompanied by extensive deoxygenation to **10** and general decomposition. Isomerization of **14** with Triton B in pyridine afforded an equilibrium mixture of sulfoxides similar in composition to the analogous sulfides **10**, **11**, and **12** obtained from **10** and Triton B. From such a mixture **16**, the *E* isomer of **15**, was isolated.



(7)

14



(8)

15

Experimental Section

General Procedures. Melting points are uncorrected and were taken on a Thomas-Hoover apparatus. Proton magnetic resonance spectra using tetramethylsilane as an internal standard were taken on Hitachi Perkin-Elmer R-24A, Varian A-60A, and JEOL C-60HL spectrometers, many by Dr. A. Douglas and Messrs. R. Zerfing and R. Reamer. Mass spectra were obtained at 70 eV on an LKB 9000 spectrometer by Mr. J. Smith. Elemental analyses were performed by Mr. J. Gilbert and his staff. Much of the gas–liquid chromatography was carried out by Mr. R. J. Phillips on a Hewlett-Packard 7620A gas chromatograph with a flame ionization detector including a 3370B integrator and 7660A multilevel temperature programmer. Tetracosane was used as an internal standard through a 6 ft × 0.125 in. stainless steel column packed with 10% SP-2401 on 100/120 mesh Supelcoport. The rest was performed on a Varian 2700 gas chromatograph with a thermal conductivity detector mated to a Hewlett-Packard integrator and using a 6 ft × 0.25 in. stainless steel column packed with 10% OV-101 on 80/100 mesh Supelcoport. Thin layer chromatography (TLC) was done on Quantum Q1-F silica gel plates and viewed under UV light. Compounds **5** (R_f 0.4–0.5) and **6** (R_f 0.9–0.95) were eluted in benzene. In 3:1 hexane–benzene **6** (R_f 0.65) is separated from its isomer **7** (R_f 0.7). Compounds **8** (R_f 0.15–0.25), **9** (R_f 0.1–0.2), **10** (R_f 0.5), and **12** (R_f 0.6) are separated with 9:1 PhH–CH_3OH. If the plate is dried and eluted a second time, then **11** (slightly slower than **10**) and **13** (slightly slower than **12**) separate. Sulfoxides **14** (R_f 0.3), **15** (R_f 0.5), and **16** (R_f 0.4) separate also in 9:1 benzene–CH_3OH. For separation of **8** (R_f 0.40) and **9** (R_f 0.25 a mixture of 25 $CHCl_3$:1 dioxane:1 CH_3CO_2H is much preferred. Spotting 5 μL of dilute solutions (≤1%) gave the best separation of components.

Direct, Colorimetric Titration of *p*-Methylthiobenzylmagnesium Chloride (3). This procedure is adapted from the elegant method of Watson and Eastham.[20]

A 125-mL filter flask was fitted with a rubber stopper carrying a nitrogen inlet and a 25-mL buret. In the flask under nitrogen were placed 20 mL of anhydrous ether, 1–2 mg of 2,2′-biquinoline as an indicator, and a magnetic stirring bar. **3** (25 mL) in ether, THF, or toluene was transferred to the indicator solution. This stirred, red-purple, thin slurry was titrated with anhydrous 1 N 2-butanol in xylene accompanied by gradual decolorization to a neutral gray and a green end point. The amount of 2-butanol required to reach the end point is equivalent to the amount of **3** in the sample.

6-Fluoro-2-methyl-3-(*p*-methylthiobenzyl)indene (6). Twenty-five grams (1.04 mol) of magnesium turnings, a crystal of iodine, and 2 mL of *p*-methylthiobenzyl chloride[21] (**2**) were stirred in 400 mL of anhydrous ether under nitrogen at reflux until Grignard formation commenced. Gentle heating (5–10 min) was usually required. A total of 39.7 g (0.23 mol, including the initial 2 mL) of **2** was added dropwise so as to maintain a gentle reflux. Refluxing was continued for 15 min. The thin precipitate present was shown in a separate experiment to be the coupled product **4**. A 25–30% solution of 5-fluoro-2-methyl-1-indanone (**1**) in toluene was added dropwise over 45–50 min at 25–35 °C to the Grignard solution with careful visual observation. At the point of contact of the indanone and Grignard solutions a transient reddish coloration appeared. This indicator effect was used to determine complete conversion of **3**. There was usually required 0.199 mol (32.6 g) of **1** and further addition gave no increase in yield. The reaction solution and suspended solids were sucked away from unreacted magnesium through a 1-mm opening in a glass pipet or dropper and the magnesium was rinsed with toluene. Over 15 min the combined reaction mixture and toluene rinse was quenched with 120 mL of 3 N sulfuric acid at 30–35 °C. The aqueous layer was discarded and the organic layer containing **5** was stirred vigorously for 1 h with 80 mL of 1:10 concentrated H_2SO_4–acetic acid. This was washed with 2 × 100 mL of water, 200 mL of 2 N NaOH, and again with water. The organic layer was concentrated under vacuum to an oil which assayed by GLC as 47.5 g (84.3% based on **1**) of **6** suitable for condensation with glyoxylic acid. By GLC **4** was measured in 10% yield.

Purification of 6. For characterization **6** was purified by dissolving 40 g of crude oil in 75 mL of 6:1 hexane–benzene. This was chromatographed through 600 g of 60–200 mesh silica gel (J. T. Baker) using the same solvent system. After 1.4–1.5 L of forerun was discarded, a rich cut of 2.4 L was concentrated to 44 g of oil which slowly crystallized from 160 mL of hexane. After filtration at 0–5 °C, washing with cold hexane, and vacuum drying at 25 °C, there was obtained 27.7 g of **6**, mp 57–59 °C. This was recrystallized from 160 mL of hexane to give 21.9 g: mp 58–60 °C; UV max 257.5 nm (ε 25 000); ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3, C_2CH_3), 2.3 (s, 3, SCH_3), 3.2 (s, 2, C_1H), 3.7 (s, 2, aromatic CH_2), 6.7–7.2 (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{17}FS$: C, 76.02; H, 6.03; F, 6.68. Found: C, 76.32; H, 5.89; F, 6.68.

1,2-Bis(*p*-methylthiophenyl)ethane (**4**) was obtained from early column chromatography fractions (see above) which were concentrated to dryness and the residue (10 g) recrystallized from toluene (2 mL/g residue) to give 2.7 g (8.6%) of **4**: mp 140–143 °C; UV max 260 nm (0.1 N HCl in CH_3OH, ε 5200); ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 6, SCH_3), 2.8 (s, 4, CH_2), 7.1 (d, 8, aromatic H).

Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61. Found: C, 70.33; H, 6.63.

When run in a similar volume of 3:1 toluene–Et_2O the yield of indene **6** was 26.6% (GLC) based on **2**, and the only other detectable product was a large quantity of **4**, 70% by GLC.

In a similar volume of 4:1 THF–toluene the yield of **6** was 23% (GLC) and **4** was estimated at 42% by GLC.

5-Fluoro-1-hydroxy-1-(*p*-methylthiobenzyl)-2-methylindan (5). Carbinol **5** was prepared by treating **3** with **1** as in the preparation of **6**, except that the reaction mixture was stirred for 2 h, during which time a heavy precipitate formed. The slurry of white solids was siphoned away from unreacted magnesium, and the slurry was filtered and thoroughly washed with ether and toluene. The cake was stirred in ether (250 mL) with 3 N H_2SO_4 (65 mL). The ether layer was washed with water, dried (Na_2SO_4), and evaporated to an oil 34.5 g. After 7 days the oil partially crystallized. The crystals were broken up and the entire mass slurried in hexane for several hours, filtered, and air dried: yield 27.3 g (39%); mp 56–61 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 and 1.1 (two doublets, 3, isomeric C_2CH_3), 2.5–2.8 (m, 3, C_2H and C_3H), 3.0 (s, 2, benzyl CH_2), 6.7–7.2 (m, 7, aromatic H); mass spectrum *m/e* 284 ($M^+ - H_2O$, 302 − 18).

Anal. Calcd for $C_{18}H_{19}FOS$: C, 71.45; H, 6.33; F, 6.28; S. 10.60. Found: C, 71.35; H, 6.54; F, 6.01; S, 10.86.

This material was recrystallized from warm hexane, recovery 72%, mp 55–60 °C.

5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)indan (7). Method A. Mother liquor solids from isolation of **6** were dissolved in an equal volume of acetone, and 5 mg of the second largest peak was isolated by preparative GLC over 10% OV-101 (230–235 °C): ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3, C_2CH_3), 2.5 (s, 3, SCH_3), 2.7–3.8 (m, 3, C_2 and C_3 H), 6.7–7.6 (m, 8, aromatic and vinyl H); mass spectrum *m/e* 284 (M^+).

Method B. To 168 mg (1.5 mmol) of *t*-BuOK in 2 mL of Me_2SO was added 651 mg (1.5 mmol) of *p*-methylthiobenzyltriphenylphosphonium chloride in 1 mL of Me_2SO followed by 270 mg (1.65 mmol) of indanone **1** in 2 mL of Me_2SO. The dark solution was heated at 75 °C for 17.5 h. By TLC some of **1** was unreacted. The reaction mixture was diluted with 10 mL of benzene and 5 mL of water, and the benzene layer was washed twice with water. The organic layer was filtered slowly through 8 g of silica gel which was also washed with benzene. The filtrate was concentrated to an oil, 372 mg. The major TLC spot was isolated by elution through 15 g of silica gel with hexene to give 96 mg of **7**, mp 67–70 °C, spectrally identical with that from Method A.

(Z)-6-Fluoro-2-methyl-3-(*p*-methylthiobenzyl)-1-indenylideneacetic Acid (10). Crude oil assaying as 11.1 g (0.039 mol) of **6** was placed under nitrogen, warmed to 42 °C, and to it was added 42.6 mL of 37.8% benzyltrimethylammonium hydroxide (Triton B; 14.73 g on a dry basis, 0.088 mol) in methanol. To this stirred, two-phase mixture at 37 °C was added 6.56 mL (4.34 g on a dry basis, 0.0586 mol, *d* = 1.313 g/mL) of 50% glyoxylic acid in water. For 45 min the reaction mixture was stirred at 50 °C. It was transferred hot to a stirred, jacketed, three-necked separatory flask and diluted with water (67 mL) and toluene (100 mL). The pH was adjusted to 2.0–2.2 with ca. 3–8 mL of H_2SO_4. With steam on the jacket the mixture was stirred at 70–75 °C until complete solution was obtained. The water layer was discarded and the washing repeated with hot water. One percent NH_4Cl (67 mL) was added and the pH adjusted to 8.5 with NH_4OH (15 mL). The toluene layer was extracted again at pH 8.5 with hot 1% NH_4Cl. To the combined aqueous extracts was added 1,2-dichloroethane (105 mL) and the temperature adjusted to 65–68 °C. The pH was adjusted to 2 with concentrated HCl and the mixture stirred at 70 °C for 1 h. The organic layer was separated, cooled, filtered, and washed to give 10 g (75%) of orange product, mp 182–184 °C. Recrystallization from hot toluene (18 mL/g) gave product in 95% recovery: mp 184–185 °C; UV max 261 nm (0.1 N HCl in CH_3OH, ε 40 500); ^{1}H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2CH_3), 2.4 (s, 3 SCH_3), 3.9 (s, 2 benzyl CH_2), 6.5 (s, 1, vinyl H), 7.0–7.4 (m, 6, aromatic H), 8.2 and 8.4 (d, 1, aromatic C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03; F, 5.58. Found: C, 70.62; H, 4.82; F, 5.48.

Irradiation of the C_2CH_3 in a degassed Me_2SO-d_6 solution gave a 49% nuclear Overhauser enhancement of the vinylic proton. This is evidence for the assigned *Z* configuration of **10**.

(E)-6-Fluoro-2-methyl-3-(*p*-methylthiobenzyl)-1-indenylideneacetic Acid (11). Mother liquors from several isolations of **10** were taken to dryness under vacuum. The residue (5.4 g) was digested in 100 ml of refluxing CCl_4 for several hours and subsequently cooled to give **11**, 1.25 g, as nearly pure material. Recrystallization two times from ethanol produced pure **11** as orange-red needles: mp 166–168 °C; UV max 260 nm (0.1 N HCl in CH_3OH, ε 41 600; ^{1}H NMR (Me_2SO-d_6) δ 2.18 (s, 3, C_2CH_3), 2.3 (s, 3, SCH_3), 3.8 (s, 2, CH_2), 6.85–7.3 (m, 3, vinyl and indene aromatic), 7.1 (s, 4, aromatic), 7.6 (m, 1, C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03. Found: C, 70.31; H, 5.25.

6-Fluoro-2-methyl-3-(*p*-methylthiobenzyl)indene-1-glycolic Acid (9). To indene **6** (20 g, 0.0704 mol) and 1,1,3,3,-tetramethylguanidine (18.2 g, 0.1585 mol) in DMF (50 mL) was added 50% glyoxylic acid (7.82 g dry basis, 0.1055 mol). The solution was heated at 52–55 °C for 1 h, quenched with 2 mL of H_2SO_4, and transferred with 75 mL of toluene to a jacketed, 500-ml, three-necked separatory funnel. Water (150 mL) was added and the pH adjusted to 2 with H_2SO_4 at 50 °C. The water layer was discarded and the hot organic layer was washed with 1% NaCl. A second portion of 1% NaCl (100 mL) was added and the pH raised to 8.5–9.0 with NaOH at >78 °C. The hot water layer was combined with 100 mL of toluene, the pH lowered to 2 with concentrated HCl, and the separated toluene layer dried by azeotropic removal of water. Product crystallized over 3 days as a fine, white solid: yield 8.26 g (32.7%); mp 179.5–181 °C; UV max 259 nm (0.1 N HCl in CH_3OH, ε 19 150); IR (CH_2Cl_2) 3550 (OH), 2900 (carboxyl OH), 1700–1725 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2CH_3), 2.4 (s, 3, SCH_3), 3.8 (s, 3, benzyl CH_2 and C_1H), 4.7 (d, 1, HCO), 6.9–7.2 (m, 7, aromatic H); D_2O exchange, δ 4.7 (s, 2, HOD).

Anal. Calcd for $C_{20}H_{19}FO_3S$: C, 67.02; H, 5.34; F, 5.30. Found: C, 66.90; H, 5.41; F, 5.20.

Compound **9** could also be isolated when the Triton B catalyzed reaction of **6** with glyoxylic acid was worked up after a few minutes of reaction.

Dehydration of 9 to 10. Attempts to dehydrate **9** under acidic conditions failed. The reagents used were I_2, HCl, or $Mg(OH)_2$ in acetic acid, and H_2SO_4 in acetic anhydride.

Dehydration of **9** to **10** was rapid with 1.5–2.0 equiv of Triton B in methanol, pyridine, or DMF at 50 °C and was followed by TLC.

(*Z*)-1-Indenylideneacetic Acid. To indene (13.5 g, 0.116 mol) under nitrogen was added tetramethylammonium hydroxide (93 mL of 2.81 M in methanol, 0.261 mol) and glyoxylic acid (19.65 mL of 50% solution in water, 0.174 mol). The reaction mixture was stirred at 55 °C for 70 min. Water (150 mL) and toluene (150 mL) were added, the pH adjusted to 2 with H_2SO_4, and the layers separated. The water layer was extracted with 2 × 50 mL of 1,2-dichloroethane, and the toluene and 1,2-dichloroethane extracts were combined. After washing with water (50 mL) the organic extracts were stripped to dryness under vacuum. The solid residue (10.4 g, 52%) crystallized from ethyl acetate (110 mL) and was dried at 50 °C under vacuum: yield 4.8 g (24%); mp 198–201 °C dec; UV max 259 nm (0.1 M HCl in CH_3OH, ϵ 27 850); TLC, single component on silica gel (9 C_6H_6–1 CH_3OH), R_f 0.35; ^1H NMR (Me_2SO-d_6) δ 6.75 (s, 1, vinyl H), 7.0–7.5 (m, 5, aromatic H and indenyl H), 7.7–7.9 (m, 1, aromatic H).

Anal. Calcd for $C_{11}H_8O_2$: C, 76.73; H, 4.68. Found: C, 76.81; H, 4.87.

(*Z*)-5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)-3-indenylacetic Acid (12). A solution of glacial acetic acid (200 mL), concentrated HCl (60 mL), and water (20 mL) was prepared. There was added 19 g (0.056 mol) of **10** and the slurry was heated at 90–95 °C for 10 h, during which the suspended solids changed from orange to yellow. The cooled mixture was filtered, washed with water, and vacuum dried at 80–90 °C to give 17.7 g (93%) of **12**, mp 180–184 °C, with <2% of either **10** or **13** by NMR. Purification was achieved by digesting 7.5 g in 38 mL of refluxing 1,2-dichloroethane for 3 h. The mixture was cooled, filtered, and washed with fresh solvent: recovery 6.5 g (87%) of single-spot material; mp 189.5–192.5 °C; UV max 350 nm (ϵ 17 500) and 258 (19 400) in 0.1 N HCl in CH_3OH; ^1H NMR (Me_2SO-d_6) δ 2.2 (s, 3, C_2 CH_3), 2.6 (s, 3, SCH_3), 3.6 (s, 2, C_3 $CH_2CO_2^-$), 6.6–7.7 (m, 8, aromatic vinyl H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03; F, 5.58. Found: C, 70.70; H, 5.02; F, 5.36.

(*E*)-5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)-3-indenylacetic Acid (13). The 1,2-dichloroethane mother liquors from several preparations of **12** were combined and partially concentrated under vacuum to collect a small second crop of **12**. The filtrate was taken to dryness in vacuo and the residue (25 g) dissolved in a small amount of benzene. Four grams of yellow solids crystallized over 2 weeks. By ^1H NMR this was comprised of a 70:30 mixture of **13**:**12** which was recrystallized three times from ethanol to give 1 g of **13**: mp 187.5–191 °C; UV max 267 and 349 nm (0.1 N HCl in CH_3OH, ϵ 20 700 and 22 200); ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.88 (s, 3, C_2 CH_3), 2.5 (s, 3, CH_3S), 3.53 (s, 2, CH_2), 7.5 (s, 1, vinyl), 6.5–7.6 (m, 3, indene aromatic), 7.25 (s, 4, aromatic).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03. Found: C, 70.50; H, 5.10.

^1H NMR Isomerization Study of 10 to 12. A solution of **10** (21 mg) in CD_2ClCD_2Cl (0.6 mL) was saturated with HCl and sealed in an NMR tube. The tube was heated at 100 °C and spectra obtained periodically over 48 h. Only peaks attributed to known compounds were observed; no evidence for a substantial population of a protonated intermediate or adduct of HCl was detected. At 70% conversion of **10** impurity peaks appeared. Compounds **10** and **12** are differentiated by their CH_2 singlets at δ 3.9 and 3.6 (Me_2SO-d_6), respectively.

Triton B Isomerization of 10 to 12 and 13. There was pipetted 0.34 mL (0.704 mmol) of 38% Triton B in methanol into 4 mL of anhydrous pyridine. This solution was stripped under vacuum to 2–3 mL, and 100 mg (0.294 mmol) of **10** was added and stirred under nitrogen at 25 °C. After 1 h TLC showed conversion largely to **12**. Two milliliters of acetic acid and some water were added. This was extracted with 1:1 benzene–ether. The organic layer was washed with 4 × 25 mL of HCl and 2 × 25 mL of 5% NaCl, then dried (Na_2SO_4) and stripped to dryness. After flushing with 2 mL of $CDCl_3$, ^1H NMR ($CDCl_3$) showed the composition to be 19% **10**, 72% **12** and 9% **13**. Similar results were obtained when isomerization was conducted in warm, methanolic Triton B.

Thermal Isomerism of 10 and 11. A crystalline sample of **11** was almost completely isomerized to **10** (TLC) when left in a melting point capillary at 130 °C for several hours. No trace of **12** or **13** was observed by TLC.

Thermal Isomerism of 12 and 13. Each isomer, **12** or **13**, was converted in NMR solvents at 110 °C to an equilibrium mixture of 82:18 of **12**:**13**. The half-lives were 45 min in pyridine-d_5 and 30 min in Me_2SO-d_6 based on the shift in the C_2 CH_3 peaks.

In the crystalline state over 18 h at 135 °C **13** was changed largely to **12**, whereas **12** remained virtually unchanged by TLC. No tautomerism to **10** or **11** was detected.

(*Z*)-6-Fluoro-2-methyl-3-(*p*-methylsulfinylbenzyl-1-indenylideneacetic Acid (14). To 1.0 g (2.94 mmol) of **10** slurried in 10 mL of $CHCl_3$ and 10 mL of acetic acid was added 0.6 mL (5.3 mmol) of 30% H_2O_2. This was stirred for 30 min and complete solution occurred. Water (40 mL) was added and the product extracted into 20 mL of 1:1 PhH/ether. The organic layer was washed four times with water, dried (Na_2SO_4), and stripped to dryness under vacuum. The crude solid (1.12 g) was crystallized from 35 mL of 50% methanol to give yellow-orange crystals: 0.905 g (86%); mp 160–163 °C; UV max 263 nm (0.1 N HCl in CH_3OH, ϵ 32 800); ^1H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2 CH_3), 2.7 (s, 3, SCH_3), 4.0 (s, 2, CH_2), 6.5 (s, 1, vinyl), 7.0 and 7.2 (d, 2, C_4 H and C_5 H), 7.4–7.7 (m, 4 aromatic), 8.2 and 8.4 (m, 1, aromatic C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_3S$: C, 67.40; H, 4.81; F, 5.33. Found: C, 67.71; H, 5.00; F, 5.14.

(*Z*)-5-Fluoro-2-methyl-1-(*p*-methylsulfinylbenzylidene)-3-indenylacetic Acid (15). To 34 g (0.1 mol) of **12** in 240 mL of 65:35 chloroform–acetic acid was added 0.103 mol of 30% hydrogen peroxide. The resulting solution was stirred at 35 °C for 4 h, at which time TLC showed reaction to be complete. After washing with water, the chloroform layer was concentrated under vacuum and the residue crystallized from ethanol to afford 32–33 g (90–92%) of product, mp 180.5–183.5 °C. Repeated recrystallization raised the melting point to 187–188 °C; UV max 256 nm (0.1 N HCl in CH_3OH, ϵ 11 400); ^1H NMR ($CDCl_3$ + CD_3OD) δ 2.2 (s, 3, C_2 CH_3), 2.8 (s, 3, SCH_3), 3.5 (s, 2, CH_2), 6.3–7.45 (m, 4, indene aromatic and vinylic), 7.7 (s, 4, benzyl aromatic); mass spectrum *m/e* (rel intensity) 357 (25), 356 (M^+, 85), 342 (24), 341 (100), 340 (17), 281 (28), 248 (39), 247 (28), 246 (39), 234 (25), 233 (89), 220 (12).

Anal. Calcd for $C_{20}H_{17}FO_3S$: C, 67.40; H, 4.81. Found: C, 67.63; H, 4.72.

Triton B Isomerization of 14. To 1.5 mL of pyridine were added 159 mg (0.446 mmol) of **14** and 0.43 mL (0.9 mmol) of Triton B (38% in CH_3OH). This was stirred for 1 h at 25 °C under N_2 and worked up by addition of 50 mL of 1:1 benzene–ether which was washed with several portions of 1 N HCl and water. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. By ^1H NMR ($CDCl_3$) it was composed of 19% **14**, 72% **15**, and 9% **16**, the *E* isomer of **15**.

(*E*)-5-Fluoro-2-methyl-1-(*p*-methylsulfinylbenzylidene)-3-indenylacetic Acid (16). Ca. 690 mg of residue enriched in **16** was chromatographed through 250 g of silica gel H with 9:1 CCl_4–CH_3CO_2H. The column was sucked dry of solvent before elution of the product, and the adsorbent was extruded in small segments. Each segment was eluted with methanol and checked by TLC. From the combined eluents of segments highly enriched in **16** a yellow solid was obtained, and it was recrystallized from 1:1 methanol–water: 47 mg; mp 178–181 °C; UV max 331 nm (ϵ 15 700), 282 (24 000), and 240 (11 500) in 0.1 N HCl in CH_3OH; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3, C_2 CH_3), 2.8 (s, 3, SCH_3), 3.5 (s, 2, CH_2), 6.55–7.8 (m, 8, aromatic and vinyl); mass spectrum *m/e* (rel intensity) 357 (11), 356 (M^+, 49), 342 (15), 341 (71), 297 (20), 281 (22), 248 (30), 247 (35), 246 (33), 234 (33), 233 (100), 220 (17).

Isomerization of 14 with Concentrated HCl–Acetic Acid. Isomerization of **14** under conditions for the isomerization of **10** to **12** results in formation (TLC) of **12** accompanied by considerable decomposition as evidenced by blackening and formation of dark, insoluble materials.

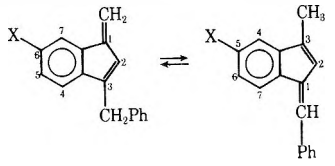
Registry No.—**1**, 41201-58-5; **2**, 874-87-3; **3**, 61812-40-6; **4**, 61812-41-7; **5**, 41201-59-6; **6**, 41201-60-9; **7**, 55507-46-5; **9**, 61812-42-8; **10**, 61812-43-9; **11**, 61812-44-0; **12**, 49627-27-2; **13**, 61812-45-1; **14**, 61849-35-2; **15**, 38194-50-2; **16**, 61812-46-2; *p*-methylthiobenzyltriphenylphosphonium chloride, 58477-22-8; glyoxylic acid, 298-12-4; (*Z*)-1-indenylideneacetic acid, 61812-47-3.

References and Notes

(1) (a) The *S*-oxide **15** is a potent antiinflammatory agent with the generic name sulindac. (b) T. Y. Shen, B. E. Witzel, H. Jones, B. O. Linn, J. McPherson, R. Greenwald, M. Fordice, and A. Jacob, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **31**, 577 (1972) (c) T. Y. Shen in "Clinoril in the Treatment of Rheumatic Disorders", E. C. Huskisson and P. Franchimont, Ed., Raven Press, New York, N.Y., 1976, p 1.

(2) Because this paper deals in part with tautomerism of a conjugated diene system comprised of an indene and an exocyclic double bond, this note

is added to clarify nomenclature. Indene is numbered beginning with the saturated carbon, C-1, of the five-membered ring. A prototropic shift must result in a new saturated carbon and, therefore, in reversal of the direction of numbering of the entire carbon skeleton. For example, a 6-subsituted



3-benzyl-1-methylideneindene upon iosmerization of both double bonds becomes a 5-substituted 1-benzylidene-3-methylindene.

(3) Generic name for 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid; a potent, widely used antiinflammatory agent.
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The Regioselective Behavior of Unsaturated Keto Esters toward Vinylogous Amides

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The regioselective reactivity of unsaturated keto ester 8 toward vinylogous amides 7 and 11 is presented, along with further evidence as to the effect of solvent on the course of the reaction.

The regioselective synthesis of indoles or quinolines from the coupling of diacyl ethylenes (**2**) and primary enamino ketones (**1**) has been reported.[1] Under acidic or neutral reaction conditions the indole derivatives (**4**) are formed whereas basic and/or dehydrogenation conditions provide the corresponding quinolines (**6**) (Scheme I). Use of an unsymmetrical

Scheme I

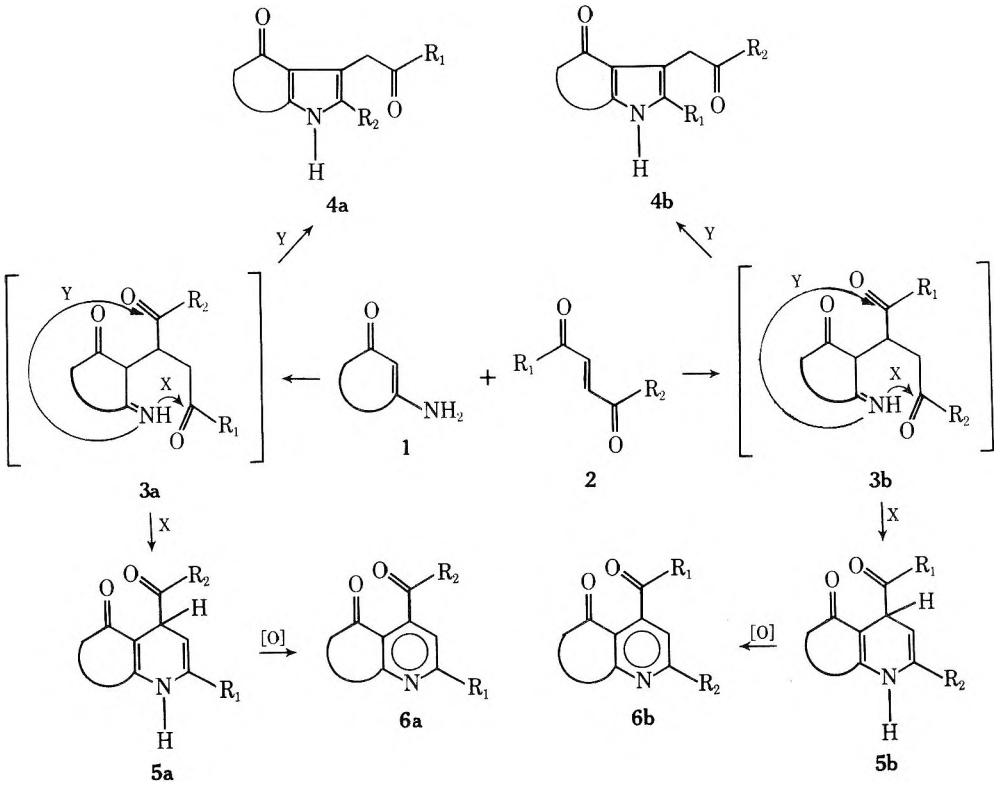


Table I. Calculated and Observed ^{13}C Absorptions Resonances[a]

	10a	10a calcd[c]	10c calcd[c]	10b
N_1CH_3[b]	28.4	28	28	28.1
C_2	150.7	150	150	150.4
N_3CH_3[b]	29.6	29	29	29.1
C_4	151.7	152	152	151.9
C_{4a}	104.5	107	111	108.3
C_5	144.7	140	156	138.0
C_6	112.7	114	107	114.7
C_7	160.5	162	152	161.5
C_{8a}	176.0	176	176	175.6
t-Bu-C	38.9	39	39	38.6
t-Bu-CH_3	29.8	30	30	30.0
CO_2CH_3	168.5	167	167	
CO_2CH_3	53.3	52	52	

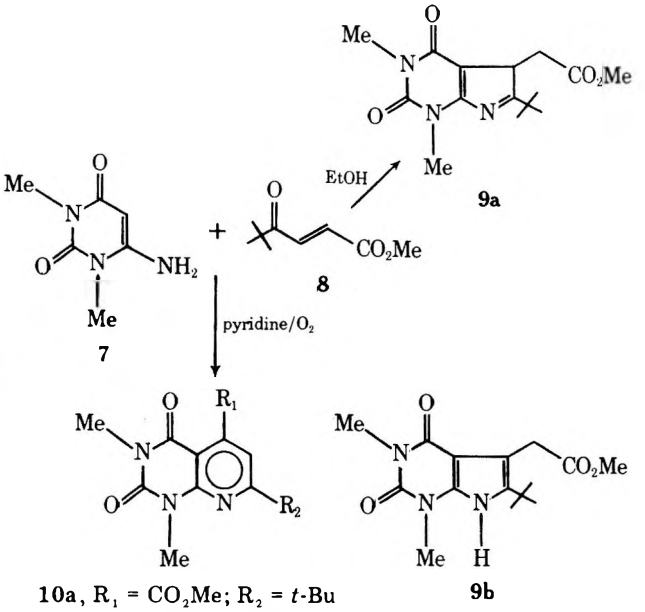
[a] Chemical shifts are reported in δ units using Me_4Si as the internal standard. [b] No distinction can be made between the absorption of N_1CH_3 and N_3CH_3. [c] The calculations were based on model compounds found in L. T. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra, A Collection of Assigned, Coded and Indexed Spectra", Wiley-Interscience, New York, N.Y., 1972.

unsaturated dicarbonyl compound (**2**, $R_1 \neq R_2$) could provide four products, **4a**, **4b**, **6a**, and **6b**. Conjugate addition 1,4 to COR_2 would lead through an intermediate such as **3b** to either **4b** or **6b** depending on the requirements for ring closure.[1] Likewise, addition 1,4 to COR_1 would provide intermediate **3a** and eventually product **4a** or **6a**.[2]

The potential for a directed process exists at two points along the reaction pathway: (1) during conjugate addition of **1** to **2** and (2) during ring closure. In the case where R_1 and R_2 are quite similar one would expect[1] a mixture of **4a** and **4b** or **6a** and **6b** depending on the reaction conditions. Based in part on the behavior of unsaturated keto esters toward such 1,3-dipolar species as diazomethane,[3] where R_1 and R_2 are dissimilar electronically, one would expect only one of the two possible isomers for each set of reaction conditions. Such is the case we wish to report.

Reaction of methyl 3-pivaloylacrylate (**8**)[4,5] and 6-amino-1,3-dimethyluracil (**7**) in refluxing pyridine provided quinoline

Scheme II



10a, $R_1 = CO_2Me$; $R_2 = t$-Bu
b, $R_1 = H$; $R_2 = t$-Bu
c, $R_1 = t$-Bu; $R_2 = CO_2Me$

10a as the only isolated product, in 36% yield. Initial nucleophilic attack on the unsaturated keto ester occurs 1,4 to the ketone. This is followed by ring closure to the ketone and not to the ester.

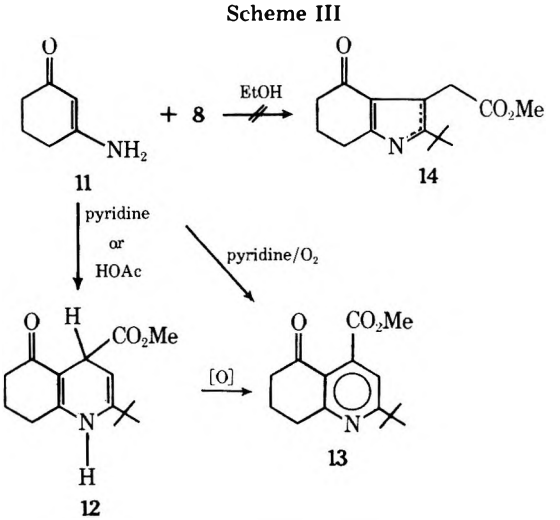
A comparison of the ^{13}C NMR spectrum of **10a** with the calculated ^{13}C NMR spectra for **10a** and **10c** helped confirm the structural assignment (see Table I). Compound **10b**, whose structure had been determined by ^{13}C NMR spectroscopy,[6] was used as the model system for these calculations.

When the same starting materials, **7** and **8**, were heated in refluxing EtOH, tetrahydroindole **9a** was isolated in only 14% yield. Once again, no other products resulting from a one-to-one combination of substrates could be observed.[7] Initial nucleophilic attack has taken place 1,4 to the ester, with subsequent ring closure to the ketone and not to the ester. That the product is isolated in the indolenine and not the indole (**9b**) tautomeric form is somewhat surprising. One rationalization for this observation would be that the indolenine form (**9a**) allows for more relief of the steric interaction between the *tert*-butyl and acetate moieties than the aromatic indole tautomer (**9b**). The assignment of structure was based on an evaluation of the product's 100-MHz ^1H NMR spectrum.

The regiospecific behavior displayed by unsaturated keto ester **8** toward vinylogous amide **7** during Michael addition is influenced by reaction conditions, whereas cyclization between imine and ketone is preferred in all cases to cyclization between imine and ester. The product composition is thus dependent upon the first step along the reaction pathway, i.e., Michael addition.

It has been reported[1] that reaction of **11**[8] and dibenzoylethylene in refluxing EtOH provides after 4 h a hexahydroquinoline of type **5** in 65% yield whereas a tetrahydroindole of type **4** is the principal product when the reaction time is extended to 48 h. In HOAc, even after short reaction times (4 h), the major product is a tetrahydroindole (**4**). These results would appear to indicate that five-membered ring formation is the thermodynamically favored process whereas six-membered ring formation can be kinetically favored. Based on these findings,[1] reaction of **8** and **11** would have been expected to provide compound **14** under acidic conditions. Exposure of vinylogous amide **11** to unsaturated keto ester **8** under nitrogen in refluxing pyridine or HOAc led only to hexahydroquinoline **12**, which could be easily oxidized to tetrahydro-

Scheme III



quinoline **13**. None of the isomeric tetrahydroindole **14** was isolated or even observed under either acidic or neutral reaction conditions. When hexahydroquinoline (**12**) was heated for several days under N_2 in either EtOH or HOAc it remained unchanged. In refluxing aqueous HOAc **12** underwent oxi-

dation to **13**. Vinylogous amide **11** clearly prefers to undergo conjugate addition 1,4 to the ketone under basic, neutral, and even acidic reaction conditions. In contrast, the reaction between enamino ketone **7** and **8** is greatly affected by solvent conditions. These findings that enamino ketones **7** and **11** should behave differently toward unsaturated keto ester **8** cannot yet be accounted for.

With the exception of those products resulting from decomposition or dimerization of starting material (30–50%) no products other than those reported could be isolated. In none of the reactions discussed was any attempt made to maximize yields. Experiments involving the use of other vinylogous amides of general structure **1** and other unsymmetrical diacylethylenes (**2**) are currently in progress. The stereochemistry of substituents about the ethylene bond of the unsaturated keto ester is a factor which significantly influences the course of such reactions and one which will also be discussed in future publications.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer Model 257 or 457 grating spectrophotometer and NMR spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C NMR spectra were recorded using a Varian XLFT-100 spectrometer as were the 100-MHz NMR spectra. Chemical shifts (δ) are recorded relative to Me_4Si; coupling constants (J) are given in hertz. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The UV spectra were obtained on a Cary Model 16 spectrophotometer. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaluation.

Methyl 3-Pivaloylacrylate (8).[5c] A. 3-Pivaloyllactic Acid. Glyoxylic acid hydrate (38.0 g, 0.41 mol) in aqueous MeOH (1:1) (2 L) was added dropwise to a solution of pinacolone (34.0 g, 0.34 mol) in H_2O (300 mL). After the addition of a solution of NaOH (27.0 g, 0.67 mol) in H_2O (60 mL), the mixture was allowed to stir at ambient temperature for 24 h, then poured into H_2O (3 L) and washed with Et_2O. The aqueous layer was acidified with concentrated HCl to pH 3 and extracted thoroughly with Et_2O. These latter Et_2O extracts were dried and evaporated to give a white solid which on recrystallization from petroleum ether provided 17.8 g (30%) of 3-pivaloyllactic acid as white crystals: mp 55–57 °C; NMR ($CDCl_3$) δ 1.10 (s, 9 H), 2.96 (AB q, J = 2, 5 Hz, 1 H), 3.10 (d, J = 5 Hz, 1 H), 3.27 (s, 1 H), 4.30 (AB q, J = 5, 5 Hz, ½ H), 4.59 (t, J = 5 Hz, ½ H), and 7.95 (broad s, exchangeable, 1 H); IR (CH_2Cl_2) 3650–2400, 1715 with shoulder at 1700 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.0; H, 7.9.

B. Methyl 3-Pivaloyllactate. A suspension of 3-pivaloyllactic acid (17.4 g, 0.1 mol), $NaHCO_3$ (9.3 g, 0.11 mol), and MeI (32 g, 0.225 mol) in DMA (125 mL) was stirred in the dark for 18 h, then poured onto H_2O (1 L). The resulting mixture was extracted with Et_2O and the combined extracts washed with brine, dried, and evaporated to give 18.0 g (96%) of crude methyl 3-pivaloyllactate as a yellow oil: NMR ($CDCl_3$) δ 1.09 (s, 9 H), 2.83–3.06 (m, 2 H), 3.22 (s, 1 H), 3.76 (s, 3 H), 4.27 (AB q, J = 5, 5 Hz, ½ H), and 4.51 (t, J = 5 Hz, ½ H); IR (CH_2Cl_2) 3540 (broad), 1750 and 1715 cm^{-1}.

C. Methyl 3-Pivaloylacrylate (8). In a flask equipped with a Dean-Stark trap, a solution of methyl 3-pivaloyllactate (18.0 g, 0.096 mol) and p-TsOH (0.2 g) in xylene (300 mL) was heated at reflux for 18 h. Evaporation of the solvent was followed by filtration of a $CHCl_3$ solution of the residue through silica gel (450 g) using 2% MeOH/$CHCl_3$ (12 L) as elutant. Distillation of the crude keto ester **8** (14.0 g) obtained by evaporation of the elutant gave 9.0 g (55%) of **8** as a yellow oil: bp 65–70 °C (0.1 mm); NMR ($CDCl_3$) δ 1.11 (s, 9 H), 3.82 (s, 3 H), 6.74 (d, J = 16 Hz, 1 H), and 7.53 (d, J = 16 Hz, 1 H); IR (CH_2Cl_2) 1735 and 1695 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 64.0; H, 8.2.

Methyl 1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-7-(dimethylethyl)pyrido[2,3-*d*]pyrimidine-5-carboxylate (10a). A continuous stream of dry air[9] was passed through a refluxing solution of unsaturated keto ester **8** (1.70 g, 10 mmol) and 6-amino-1,3-dimethyluracil (**7**, 1.55 g, 10 mmol) in pyridine (45 mL) for 12 h. After cooling, the mixture was evaporated to dryness and the residue dissolved in $CHCl_3$ and filtered through silica gel (300 g). Elution with $CHCl_3$ (2 L) provided a white, crystalline material on evaporation of the solvent. Recrystallization from a minimum of Et_2O gave 1.1 g (36%) of **10a** as white crystals: mp 109.5–111 °C; NMR (XL-100) ($CDCl_3$) δ 1.41 (s, 9 H), 3.42 (s, 3 H), 3.73 (s, 3 H), 4.01 (s, 3 H), and 7.16 (s, 1 H); IR ($CHCl_3$) 1745, 1715, and 1670 cm^{-1}.

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.0; H, 6.3, N, 13.8. Found: C, 59.0; H, 6.2; N, 13.6.

Methyl 6-(Dimethylethyl)-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-1*H*-pyrolo[2,3-*d*]pyrimidine-5-acetate (9a). To a solution of unsaturated keto ester **7** (10.2 g, 0.06 mol) in EtOH (200 mL) was added aminouracil **8** (9.3 g, 0.06 mol) and the mixture was heated at reflux for 16 h, then cooled to ambient temperature and filtered. Evaporation of the filtrate provided a white solid, which on recrystallization from a minimum of Et_2O gave 2.5 g (14%) of **9a**: mp 144–146 °C; NMR (XL-100) ($CDCl_3$) δ 1.25 (s, 9 H), 2.32 (AB q, J = 9, 15 Hz, 1 H), 3.22 (AB q, J = 3, 15 Hz, 1 H), 3.39 (s, 3 H), 3.57 (s, 3 H), 3.69 (s, 3 H), and 3.85 (AB q, J = 3, 9 Hz, 1 H); IR ($CHCl_3$) 1740, 1710, 1660, and 1600 cm^{-1}; UV (EtOH) 325 nm (ϵ 4273) and 218 (14 079).

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.6; H, 6.9; N, 13.7. Found: C, 58.8; H, 7.1; N, 13.2.

Methyl 2-(Dimethylethyl)-1,4,5,6,7,8-hexahydro-5-oxoquinoline-4-carboxylate (12). A solution of vinylogous amide **11**[8] (11.1 g, 0.1 mol) and unsaturated keto ester **8** (17.0 g, 0.1 mol) in HOAc (150 mL) was heated at reflux under N_2 for 48 h. Evaporation of the solvent and partition of the residue between Et_2O and saturated aqueous $NaHCO_3$ provided, after evaporation of the brine-washed Et_2O phase, an oil of one spot purity which crystallized on standing. Trituration with a minimum of Et_2O gave 9.56 g (36.3%) of **12** as white crystals: mp 172–174 °C; NMR)cdcl$_3$) δ 1.10 (s, 9 H), 1.84–2.60 (m, 6 H), 3.64 (s, 3 H), 4.25 (d, J = 4 Hz, 1 H), 4.65 (d of d, J = 1.5, 4 Hz, 1 H), and 6.42 (broad s, exchangeable, 1 H); IR ($CHCl_3$) 3455, 1740, 1680 (w), and 1620 cm^{-1}; UV (EtOH) 343 nm (ϵ 3873), 233 (4052), and 214 (4039).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.2; N, 8.0; N, 5.2.

Methyl 2-(Dimethylethyl)-5,6,7,8-tetrahydro-5-oxoquinoline-4-carboxylate (13). A. From 12. To a solution of hexahydroquinoline **12** (9.15 g, 0.035 mol) in xylene (500 mL) was added 10% Pd/C (0.5 g) and the suspension was heated at reflux for 18 h. After filtration through Celite, evaporation of the filtrate gave a white solid. Recrystallization from Et_2O afforded 4.0 g (44%) of tetrahydropyridine **13**: mp 139.5–40.5 °C; NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.19 (d of q, J = 6 Hz, 2 H), 2.67 (broad t, J = 6 Hz, 2 H), 3.22 (broad t, J = 6 Hz, 2 H), 3.96 (s, 3 H), and 7.22 (s, 1 H); IR ($CHCl_3$) 1740 and 1690 cm^{-1}; UV (EtOH) 283 nm (ϵ 3632) and 233 (3680).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.4. Found: C, 69.2; H, 7.5; N, 5.3.

B. From 8. Following the procedure described to prepare **10a**, but using vinylogous amide **11** in place of **7**, gave a 24% yield of **13**, mp 138.5–140 °C.

Acknowledgment. Those services provided by the Analytical Section of the Medicinal Chemistry Department are gratefully acknowledged. In particular the ^{13}C NMR calculations of Ms. R. Mansukhani are appreciated.

Registry No.—**7**, 6642-31-5; **8**, 34553-31-6; **9a**, 61689-27-8; **10a**, 61689-28-9; **11**, 5220-49-5; **12**, 61689-29-0; **13**, 61689-30-3; glyoxylic acid, 298-12-4; pinacolone, 75-97-8; 3-pivaloyllactic acid, 61689-31-4; MeI, 14-88-4; methyl 3-pivaloyllactic acid, 61689-32-5.

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mization, every effort was made to ensure that, other than those products resulting from decomposition of the starting materials,[10] no reaction products isomeric with those isolated were present in the crude reaction-product mixtures. In all cases greater than 95% of the material balance has been accounted for.

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The Effect of Lewis Acids on Stereoselectivities in Ketone Reductions. The Principle of Complexation-Induced Conformational Perturbation. Energy Minimization in the Transition States for Hydride Transfer[1]

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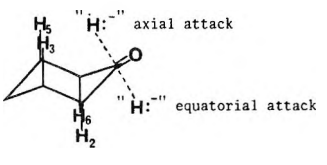
Stereochemical results from reductions of alkyl-substituted cyclohexanones by organosilanes in boron trifluoride etherate and in aqueous sulfuric acid demonstrate that Lewis acid complexation with the carbonyl oxygen plays a major role in determining product stereoselectivity. These results, together with similar changes in stereoselectivity due to variations in the metal ion employed in Meerwein–Ponndorf–Verley, borohydride, and aluminum hydride reductions, lead to the proposal that stereoselectivity in ketone reductions is a function of the size of the complexing agent and the degree of association between the carbonyl oxygen and the complexing agent in the transition state for hydride transfer. To explain the "4-methyl, 4-*tert*-butyl effect" and the "2-methyl effect" the principle of complexation-induced conformational perturbation is introduced. According to this tenet, the reacting complexed ketone adopts a conformation that minimizes steric (or torsional) interactions in the transition state for hydride transfer. Stereochemical and kinetic data are consistently explained by application of this principle. Stereochemical results from reductions of model ketones, *trans*-1-decalone and *trans*-2-decalone, are reported; these results are consistent with the transition state model for complexation-induced conformational perturbation but are opposite to those predicted from the conformational equilibrium model. The effects of the postulate that hydride transfer preferentially occurs to minimize interactions between the incoming hydride and the complexed ketone on the currently held models for stereoselectivity in nucleophilic addition reactions are discussed.

The predominance of one stereoisomeric product in nucleophilic additions to ketones depends on the nature of the nucleophile, on the stereochemical relationship between the reactants during addition, and on the intricate details of the reaction pathway.[3] The evolution of current understanding of stereoselectivity in these reactions has occurred primarily through studies of cyclic ketones.[4,5] A wealth of data on stereoselective hydride reductions of cyclic ketones exists and is interpreted with general acceptance[5] in terms of a combination of steric and torsional interactions between the substrate and the reducing agent in the transition state for hydride transfer as well as by electronic influences emanating from polar substituents remote from the carbonyl group. Conformational[6] and molecular orbital[7] influences on stereoselectivity in cyclic ketone reductions have recently been proposed.

Steric approach control,[4b] which implies that the transition state resembles the reactants in geometry, is widely believed to govern the course of ketone reductions by hydride reducing agents. Furthermore, hydride transfer is understood to preferentially occur when the ketone is in its most stable conformation and, to effect maximum overlap in the transition state, hydride approaches the carbonyl carbon along a line perpendicular to the plane of the carbonyl group.[7e,8]

When these criteria are applied to reductions of substituted cyclohexanones, for example, a distinct picture of stereoselective control emerges (structure 1). Axial hydride attack is subject to steric interactions from atoms or groups of atoms on the axial 3,5 positions. Equatorial hydride attack is subject to torsional interference with the axial 2,6 hydrogens. The stereoselectivity of hydride transfer to substituted cyclohexanones is believed to be determined by the relative magnitude of these steric and torsional interactions.[5]



1

Recent stereochemical data on reductions of cyclohexanones by numerous aluminum hydride,[4h,9] borohydride,[10] and organosilane[1,6d,11] reagents have generated several questions that cannot be explained by the account of stereoselective control outlined in structure 1. The "2-methyl effect",[6a] in which the relative yields of the less stable cis isomer from reductions of 2-methylcyclohexanone are substantially greater than those from 4-*tert*-butylcyclohexanone, requires modification of the currently held view of stereoselectivity. The complex "4-methyl, 4-*tert*-butyl effect" is even more difficult to understand. Here, the relative yield of the less stable cis alcohol from reductions of 4-methylcyclohexanone is greater than that from 4-*tert*-butylcyclohexanone when sterically small reducing agents are employed, but this phenomenon is reversed when sterically large reducing agents are used.

In the course of our investigations of stereoselectivity in ketone reductions by organosilanes we have found that the nature of the Lewis acid catalyst has a major effect.[1] In this paper we assign to Lewis acid complexation an integral role in the control of reduction stereoselectivity. We will describe the stereochemical relationship between the reactants in the process of reduction in terms of "complexation-induced conformational perturbation" of the ketone in the transition state. This new principle of stereoselective control unravels the "2-methyl effect" and the "4-methyl, 4-*tert*-butyl effect", satisfactorily explains the results from hydride reductions and nucleophilic additions of cyclic ketones, and predicts the stereochemical course of these reactions more successfully than previous theories.

Table I. Stereoselectivities of Organosilane Reductions of Alkyl-Substituted Cyclohexanones in Aqueous Sulfuric Acid and in Boron Trifluoride Etherate[a]

Registry no.	Cyclohexanone	Relative yield, % less stable alcohol from reduction by n-$BuSiH_3$		Et_2SiH_2		Et_3SiH	
		BF_3-Et_2O[b]	H_2SO_4[c]	BF_3-Et_2O[b]	H_2SO_4[c]	BF_3-Et_2O[d]	H_2SO_4[c]
98-53-3	4-*tert*-Butyl-	17	10	36	20	61	32
589-92-4	4-Methyl-	19	18	39	26	60	35
591-24-2	3-Methyl-	24	19	48	29	67	39
583-60-8	2-Methyl-	34	31	52	41	64	54
873-94-9	3,3,5-Trimethyl-	87	74	91	85	95	90

[a] Reactions were run at room temperature (25 ± 2 °C). [b] Molar ratio of boron trifluoride etherate to ketone was 1:1. Alcohols were the only products observed after basic hydrolysis. [c] Data taken from ref 6d. [d] Data taken from ref 1.

Table II. Stereoselectivity in Triethylsilane Reductions of 4-*tert*-Butylcyclohexanone Promoted by Lewis Acid Catalysts

Registry no.	Acid	Alcohol derivative	% cis isomer	$k_{axial}/k_{equatorial}$
76-05-1	CF_3COOH[6d]	Trifluoroacetate	32	0.47
7664-93-9	H_2SO_4, H_2O[6d]	Alcohol	32	0.47
64-18-6	$HCOOH$[1]	Formate	38	0.61
7772-99-8	$SnCl_2$[1]	Alkyl silyl ether	42	0.72
7446-70-0	$AlCl_3$[1]	Alkyl silyl ether	60	1.50
7637-07-2	BF_3[1]	Borate ester[b]	61	1.56
56889-93-1	*trans*-4-*tert*-Butylcyclohexyl[6d,a]	Symmetrical ether	63	1.7
56889-94-2	*cis*-4-*tert*-Butylcyclohexyl[6d,a]	Symmetrical ether	84	5.2

[a] Reduction of $R_2C{=}{}^+OR'$ leading to symmetrical ethers during triethylsilane reduction of 4-*tert*-butylcyclohexanone in trifluoroacetic acid. [b] Analyzed as alcohol.

Results and Discussion

Effect of Lewis Acid Complexation on Stereoselectivity in Cyclic Ketone Reductions. Table I presents the stereochemical results from reductions of alkyl-substituted cyclohexanones by alkylsilanes in boron trifluoride etherate and compares these results with those from the corresponding reactions in aqueous sulfuric acid. Cyclohexanones are rapidly reduced by organosilanes in BF_3-Et_2O to borate esters

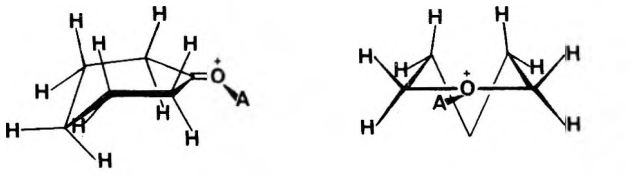
$$3R_2C{=}O + 3R'_3SiH + BF_3 \rightarrow (R_2CHO)_3B + 3R'_3SiF \quad (1)$$

which are, in turn, conveniently hydrolyzed to alcohols during product isolation from aqueous base. The mechanism of ketone reductions in BF_3-Et_2O is suggested to involve hydrosilylation of the boron trifluoride activated carbonyl group followed by fluoride displacement at silicon and has been previously discussed.[1]

Table I clearly shows that stereoselectivity depends on the acid employed in cyclic ketone reductions by organosilanes. Not only do the relative yields of the less stable alcohol isomers increase with increasing size of the reducing agent (steric approach control) but, also, a substantial increase in the relative yield of the less stable alcohol isomer is obtained when the size of the Lewis acid is increased from "H^+" (aqueous H_2SO_4) to BF_3 (BF_3-Et_2O). A similar effect on stereoselectivity has been noted in $AlCl_3$-, $ZnCl_2$-, and $SnCl_2$-catalyzed organosilane reductions of 4-*tert*-butylcyclohexanone.[1] In addition, reductions of oxonium ions of the type $R_2C{=}{}^+OR'$ ($R_2C{=}O$ = 4-*tert*-butylcyclohexanone, R′ = *cis*- and *trans*-4-*tert*-butylcyclohexyl) to ethers by organosilanes are highly sensitive to the nature of R′.[6d] Table II summarizes the dependence of reduction stereoselectivity on Lewis acids by presenting the ratio of the relative rates for axial and equatorial attack by triethylsilane on Lewis acid complexed 4-*tert*-butylcyclohexanone. Clearly the Lewis acid plays an integral role in the control of stereoselectivity in organosilane reductions.

The increase in equatorial attack in cyclohexanone reductions that is caused by changes in the Lewis acid is not limited to organosilane reagents. Recent stereochemical results from several laboratories, involving a wide range of hydride reducing agents, point to the same dependence. In the Meerwein–Ponndorf–Verley reductions of substituted cyclohexanones and steroidal ketones, changing from lithium to sodium to potassium isopropoxide substantially increases the yields of the less stable alcohol isomers.[12] Similarly, in cyclic ketone reductions by tri-*sec*-butyl borohydride, the potassium salt[13] favors the less stable alcohol isomer more than does the lithium salt;[10c] similar results are reported for lithium and sodium borohydride reductions of alkylcyclohexanones.[14] Stereoselectivity in aluminum hydride reductions is likewise subject to the nature of the metal salt.[6a] Although these results can be explained by proposing changes in the effective sizes of the individual reducing agents, we believe that they are more properly and harmoniously ascribed to conformational changes in the reacting ketone due to complexation of the Lewis acid (or metal ion) with the carbonyl oxygen in the transition state for hydride transfer. This complexation activates the carbonyl group for hydride transfer and stabilizes the resulting alkoxide.

Complexation-Induced Conformational Perturbation. Three basic postulates underlie the theories that have been developed to explain stereoselectivity in ketone reductions: (a) that steric approach control governs the course of ketone reductions by hydride reducing agents, (b) that the hydride approaches perpendicular to the carbonyl group,[8] and (c) that hydride transfer preferentially occurs when the ketone is in its most stable conformation (which is usually defined as the most stable ground state conformation[4,5]). When laid upon these foundations at least four reaction parameters are identified as controlling stereoselectivity during hydride attack at the carbonyl carbon of cyclic ketones: (1) the size of the nucleophile, (2) the "nucleophilicity" of the attacking reagent, (3) steric interactions between the cyclic ketone and the attacking reducing agent, and (4) torsional strain (or gauche hydrogen–hydrogen interactions[15]) between the incoming hydride and suitably positioned α hydrogens.[4,5] Except for the recent proposal of a conformational equilibrium



3a 3b

Figure 1. Complexation-induced ring flattening of cyclohexanone: view from the side (**3a**) and view along the carbonyl group (**3b**).

model to explain the 2-methyl effect,[6] the attributes of complexation between the carbonyl oxygen of ketones and a Lewis acid or metal ion in effecting stereochemical control of hydride transfer have been generally overlooked.

We propose that stereoselectivity in ketone reductions is a function of the size of the complexing agent and of the degree of association between the carbonyl oxygen of the ketone and the complexing agent in the transition state for hydride transfer. This complexation initially results in steric (or torsional) interference between the complexing agent and α substituents of the ketone. With cyclohexanone in particular, the complexing agent (A) and substituents on the equatorial 2,6 positions are nearly eclipsed or sterically encumbered when cyclohexanone is in its chair conformation (structure **2a**). To relieve this strain *the complexed ketone adopts a conformation that minimizes steric (or torsional) interactions in the transition state for hydride transfer.* In the case of cyclohexanone, complexation induces a flattening of the ring about the carbonyl group (structure **2b**). The extent of ring flat-

2a 2b

tening in the transition state is dependent on the flexibility of the ketone, on the size and degree of association of A with the carbonyl oxygen, on the nature and size of α substituents, and on the reactivity of the hydride reducing agent. Complexation may occur prior to hydride transfer, as in organosilane reductions,[1,11] or be concurrent with hydride transfer, as appears likely in ketone reductions by lithium aluminum hydride.[16] In either case, *complexation activates the carbonyl group for hydride transfer, stabilizes the developing alkoxide ion, and induces a change in the conformation of flexible*[17] *ketones.*

Ground state flattening of cyclohexane rings from the idealized model having bond angles of 109.5° and torsional angles of 60° is well documented.[18-20] Electron diffraction and x-ray analyses of substituted cyclohexane derivatives suggest that the cyclohexane ring is flexible to conformational distortions. Torsional angles around the bonds adjacent to the carbonyl group are contracted appreciably in comparison with the idealized model.[20] Further flattening of the cyclohexanone ring is, therefore, a reasonable consequence of complexation between the carbonyl group and a Lewis acid in the transition state for hydride transfer.

Structures **3a** and **3b** in Figure 1 exemplify the consequences of complexation-induced ring flattening for hydride attack on cyclohexanones. In structure **3** C_5, C_6, C_1, C_2, and C_3 all lie in the same plane; however, this conformation is but one complexation-induced conformational possibility between the chair and boat conformational extremes for cyclohexanone. Flattening of the cyclohexanone ring produces increased "gauche → eclipsed" interactions between hydrogens on 2,6 and 3,5 positions and between C_1–C_2, C_1–C_6 and C_3–C_4, C_5–C_4, but these effects are counteracted by the decreased interactions between A and "equatorial" 2,6 hydrogens. Structure **3** represents that conformation in which interactions between A and substituents on the 2 and 6 positions are minimized. Noteworthy is the inward compression of axial 3,5 hydrogens which leads to an increase in this long-range 1,3-diaxial interaction but effects a decrease in short-range torsional strain between "equatorial" 2,6 hydrogens and axial 3,5 hydrogens. For axial hydride attack flattening of the cyclohexanone ring leads to increased interactions of the incoming hydride with "equatorial" 2,6 hydrogens and to decreased interactions with axial 3,5 hydrogens (steric interference[4e]). Likewise, for equatorial hydride attack there is an increase in the long-range interaction between the incoming hydride and the axial 4 hydrogen but, also, a slight decrease in interactions with "axial" 2,6 hydrogens (torsional strain[4f,g,15]).

Ring flattening of cyclohexanones during reduction or nucleophilic addition reactions has recently been promoted by Anh and co-workers as a factor favorable to axial attack.[21] Our analysis does not provide such a clear-cut distinction. Indeed, the protraction of "axial" 2,6 hydrogens due to ring flattening leads to little change or a slight decrease in interactions of these hydrogens with an incoming hydride, while contraction of the "equatorial" 2,6 hydrogens suggests that an incoming hydride will encounter increased interactions with these hydrogens.

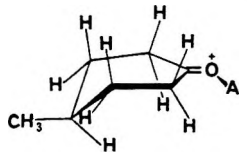
Participation of the flexible conformation of cyclohexanones in chemical reductions has also been suggested to explain reaction stereoselectivities.[22] However, the flexible cyclohexanone conformation does not offer any advantage over the chair conformation in minimizing interactions between α substituents and A.

The postulate of complexation-induced flattening of the cyclohexanone ring in the transition state for hydride transfer retains those four reaction parameters that were previously discussed as playing an integral role in controlling stereoselectivity. However, our proposal modifies one of the basic postulates that underlies stereoselectivity arguments—that hydride transfer preferentially occurs when the ketone is in its most stable conformation. Application of the modified postulate, that *hydride transfer preferentially occurs to minimize interactions between the incoming hydride and the complexed ketone,* leads to the inference that as the transition state for hydride transfer approaches structure **3** the forces between the reducing agent and the substrate can be divided into two categories: short-range effects and long-range effects. Interactions of the incoming hydride with "axial" 2,6 hydrogens and with "equatorial" 2,6 hydrogens comprise short-range effects and are responsible for the stereoselectivities obtained in reductions of cyclohexanones by small reducing agents such as sodium borohydride, lithium aluminum hydride, and *n*-butylsilane. Interactions with axial 3,5 hydrogens and with the axial 4 hydrogen comprise long-range effects which, together with short-range effects, affect the stereoselectivities in reductions of cyclohexanones by bulky reducing agents such as the tri-*sec*-butyl borohydrides[10c,13] or di-*tert*-butylmethylsilane.[11a] This stereochemical model is significantly different from that used by Marshall[4e] and, as will be discussed next, provides a uniform explanation for the "4-methyl, 4-*tert*-butyl effect".

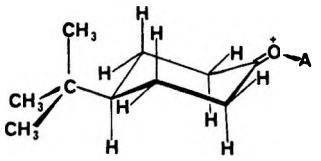
Table III compares the relative yields of the less stable cis-alcohol isomers from reductions of 4-*tert*-butylcyclohexanone and 4-methylcyclohexanone by representative aluminum hydride, borohydride, and organosilane reagents. With small reducing agents such as diborane, *n*-butylsilane, lithium aluminum hydride, and sodium borohydride,[24] the relative yields of the less stable cis alcohol isomer from reductions of 4-*tert*-butylcyclohexanone are less than those from reductions of 4-methylcyclohexanone. However, as the steric bulk of the

reducing agent is increased, there is a reversal in the relative yields of the cis-alcohol isomers; reductions of 4-*tert*-butylcyclohexanone by bulky trialkyl borohydrides and trialkylsilanes give a greater percentage of cis alcohol than do reductions of 4-methylcyclohexanone.

This "4-methyl, 4-*tert*-butyl effect", although reflecting small energy differences, is adequately explained by application of the principle of complexation-induced conformational perturbation. Ring flattening of complexed 4-*tert*-butylcyclohexanone during hydride transfer is hindered by steric interactions between the *tert*-butyl group and axial 3,5 hydrogens. No such hindrance to ring flattening can be expected from the methyl group of 4-methylcyclohexanone. Thus from our earlier consideration of short-range effects in reductions of complexed ketones, we can predict that the yield of the less stable alcohol isomer will be less in reductions of 4-*tert*-butylcyclohexanone than in reductions of 4-methylcyclohexanone—exactly what is observed. However, the stereoselectivities in reductions of 4-methylcyclohexanone by bulky reducing agents, in which long-range effects are also operative, are influenced by decreased interaction between the incoming hydride and axial 3,5 hydrogens and by increased interference from the axial 4 hydrogen, relative to reductions of 4-*tert*-butylcyclohexanone (structures **4a** and **4b**).[20a] Compared to reductions of 4-*tert*-butylcyclohexanone



4a



4b

by the same bulky reducing agents both of these long-range interactions favor axial hydride attack leading to the equatorial alcohol.[20b]

Similar considerations of complexation-induced ring flattening of cyclohexanones explain the general observation of higher yields of the less stable alcohol isomer in reductions of 3-methylcyclohexanone when compared to reductions of 4-*tert*-butylcycohexanone. Although ring flattening of 3-methylcyclohexanone causes increased interaction between the "axial" 2-hydrogen and the equatorial 3-methyl group and leads to further inward compression of the axial 3,5 hydrogens compared to cyclohexanone, in the chair conformation for 3-methylcyclohexanone the equatorial 3-methyl substituent increases steric interference of the equatorial 2 hydrogen with the complexing agent ("gauche-butane"-like interactions[15,26,27]) and promotes ring flattening.

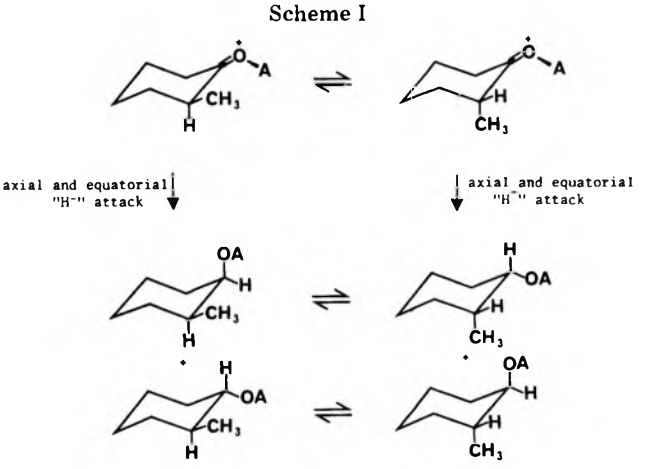
2-Methyl Effect. The "2-methyl effect" in reductions of 2-methylcyclohexanones has received considerable attention in recent years.[6] Evidence has been presented to suggest that there is significant participation of the less stable chair conformer in the transition state for reduction of 2-methylcyclohexanone.[6a-c] Model compounds for the equatorial chair conformer of 2-methylcyclohexanone, *cis*-4-*tert*-butyl-2-methylcyclohexanone,[6a] and 2,4,4-trimethylcyclohexanone[6c] have been used to determine the extent of involvement of the equatorial and axial chair conformers in the transition state for reduction by hydride reagents. To explain the accumulated data the reduction of 2-methylcyclohexanone is represented as occurring through hydride attack on both the axial and equatorial conformers (conformational equilibrium model, Scheme I). Prior or concurrent association of the complexing agent (A) with the carbonyl group increases the relative proportion of the associated axial conformer in the transition state for hydride transfer.[6a] This interpretation for the

Table III. Stereoselectivities in Hydride Reductions of 4-*tert*-Butylcyclohexanone and 4-Methylcyclohexanone

Reducing agent	Relative % cis isomer from reduction of 4-*tert*-Butylcyclohexanone	Relative % cis isomer from reduction of 4-Methylcyclohexanone
B_2H_6[23]	10	15
$LiAlH(O\text{-}t\text{-}Bu)_3$[9a]	10	14
$n\text{-}BuSiH_3$, H^+ [6d]	10	18
$LiAlH_4$, Et_2O[9b,10b]	11	17
$NaBH_4$, *i*-PrOH	12, 14[10g]	15,[10f] 14[10g]
$n\text{-}BuSiH_3$, BF_3	17	19
Et_2SiH_2, H^+ [6d]	20	26
Et_3SiH, H^+ [6d]	32	35
Et_2SiH_2, BF_3	36	39
$1PC_2BH$[a,10b,25]	37	33
LiPBPH[b,10b]	54	52
Et_3SiH, $BF_3\text{-}Et_2O$[1]	61	60
$(t\text{-}Bu)_2MeSiH$, H^+ [11a]	72	67
Li-*sec*-Bu_3BH, 0 °C[10c]	93	80
$LiSia_3BH$, −78 °C[10h]	>99.5	99.0

[a] Diisopinocampheylborane. [b] Lithium perhydro-9b-borophenalylhydride.

Scheme I



stereoselectivities that are observed in reductions of 2-methylcyclohexanone differs markedly from our proposal of complexation-induced conformational perturbation.

The principle of complexation-induced conformational perturbation predicts that ring flattening of 2-methylcyclohexanone will occur in the transition state for hydride transfer. Ring flattening decreases steric interactions between the complexing agent and the "equatorial" 2-methyl group but, also, increases steric interactions between the incoming hydride and the "equatorial" 2-methyl group in the transition state for axial attack (structure **5**). Increasing the size of the

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complexing agent magnifies these steric interactions by increasing the $CH_3\text{–}C_2\text{–}C_1\text{=}^+OA$ dihedral angle and leads to an increase in the relative yield of the less stable cis alcohol—exactly what is observed. However, although both this model and the conformational equilibrium model predict the same stereochemical results for reductions of 2-methylcyclohexa-

Table IV. Stereoselectivities in Reductions of 2-Methylcyclohexanone and Conformational Models for 2-Methylcyclohexanone

Reducing agent	Relative % less stable alcohol from reduction of 2-Methylcyclohexanone	*trans*-1-Decalone	4-*tert*-Butylcyclohexanone	*cis*-4-*tert*-Butyl-2-methylcyclohexanone
$LiAlH_4$, THF[6a]	24	26[a,b]	10	17 (17)[a,b]
$ClMgAlH_4$, THF[6a]	36		10	21
$Mg(AlH_4)_2$, THF[6a]	49		13	27
$NaBH_4$, *i*-PrOH	31[6c]	37[a] (32)[c,d]	12[a]	21[a]
n-$BuSiH_3$, H^+ [6d]	31	34[a]	10	19[a]
n-$BuSiH_3$, BF_3[a]	34	42	17	25
Et_2SiH_2, H^+ [6d]	41	44[a]	20	31[a]
Et_2SiH_2, BF_3[a]	52	58	36	43
Et_3SiH, H^+ [6d]	48	48[a]	32	39[a]
Et_3SiH, BF_3[1]	64	65[a]	61	54[a]

[a] This work. [b] Ethyl ether solvent, 0 °C. [c] Reduction in methanol, ref 28. [d] Reduction of 2,4,4-trimethylcyclohexanone yields 18% of the less stable cis isomer.

Table V. Stereoselectivities in Reductions of *trans*-2-Decalone and 3- and 4-Methylcyclohexanones

Reducing agent	Relative % less stable alcohol from reduction of 3-Methylcyclohexanone	4-Methylcyclohexanone	*trans*-2-Decalone
$LiAlH_4$	16[10b]	17[10b]	18[a]
n-$BuSiH_3$, H^+	19[6d]	18[6d]	18
Et_3SiH, H^+	39[6d]	35[6d]	39
Et_3SiH, BF_3	67[1]	60[1]	64

[a] Ethyl ether solvent, 0 °C.

none, they differ significantly in their predictions of the stereochemical outcome for reductions of *trans*-1-decalone.

The stereoselectivities for reductions of *trans*-1-decalone are predicted by the conformational equilibrium model to be nearly identical with those of *cis*-2-methyl-4-*tert*-butylcyclohexanone or 2,4,4-trimethylcyclohexanone, since in each of these three ketones the 2-alkyl group is essentially locked in the equatorial position. The yield of the less stable alcohol isomer from reductions of *trans*-1-decalone is, therefore, predicted to be significantly less than that found in reductions of 2-methylcyclohexanone.

In contrast, the principle of complexation-induced conformational perturbation predicts that the relative yield of the less stable alcohol isomer from reductions of *trans*-1-decalone will be at least as great as the relative yield of *cis*-2-methylcyclohexanol from reductions of 2-methylcyclohexanone. Ring flattening about the carbonyl group of *trans*-1-decalone is not restricted by the ring fusion and should occur to nearly the same extent as in reductions of 2-methylcyclohexanone. However, because of the "3-alkyl" substituent on the cyclohexanone ring of *trans*-1-decalone, which also promotes ring flattening in the transition state for hydride transfer, the relative yield of the less stable axial isomer from *trans*-1-decalone reductions is expected to be slightly greater than the relative yield of *cis*-2-methylcyclohexanol.

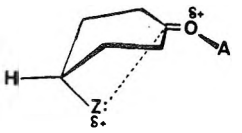
Table IV presents the stereochemical results from reductions of *trans*-1-decalone and 2-methylcyclohexanone and compares these yields with those from reductions of 4-*tert*-butylcyclohexanone and *cis*-4-*tert*-butyl-2-methylcyclohexanone. Clearly, the relative yields of the less stable alcohol isomer from reductions of *trans*-1-decalone are at least as great as or greater than those from reductions of 2-methylcyclohexanone. The data in Table IV are consistent with the predictions of stereoselectivity that are based on the complexation-induced ring flattening model but markedly disagree with those based on the conformational equilibrium model.

Hydride reduction of *cis*-4-*tert*-butyl-2-methylcyclohexanone gives lower yields of the less stable alcohol isomer than does hydride reduction of 2-methylcyclohexanone because the 4-*tert*-butyl group restricts ring flattening. Indeed, it is noteworthy that the yield of the less stable alcohol from reductions of *cis*-4-*tert*-butyl-2-methylcyclohexanone falls approximately midway between the corresponding alcohol yields from reductions of 2-methyl- and 4-*tert*-butylcyclohexanones. For reductions of complexed *cis*-4-*tert*-butyl-2-methylcyclohexanone the effects on energy minimization by the 4-*tert*-butyl and 2-methyl groups are opposed in the transition state for hydride transfer: the 2-methyl group promotes ring flattening while the 4-*tert*-butyl group hinders ring flattening.

Consideration of the principle of complexation-induced conformational perturbation for reductions of 2,4,4-trimethylcyclohexanone also results in the prediction that the relative yield of the cis-alcohol product will be less than the relative yield of *cis*-2-methylcyclohexanol from reductions of 2-methylcyclohexanone. The axial 4-methyl substituent does not restrict ring flattening. However, ring flattening presses the axial 4-methyl group close to the carbonyl group and leads to an increase in steric hindrance to hydride attack that results in the less stable alcohol isomer.

The conformational equilibrium model has also been used to explain the stereoselectivities in reductions of 3-alkylcyclohexanones.[6d,10a] However, as can be seen from the stereochemical data in Table V, there is little or no difference in the percent yields of the less stable alcohol isomers from reductions of 3-methylcyclohexanone and *trans*-2-decalone. Thus, the conformational populations of the reactant ketones do not measurably influence reduction stereoselectivity. The complexation-induced conformational perturbation model correctly predicts the observed stereochemical results.

The principle of complexation-induced conformational perturbation unifies diverse results that have been previously explained by the conformational equilibrium model or by electrostatic effects from remote substituents.[5,28,29] Application of this principle to the kinetic and stereochemical results obtained by Kwart and Takeshita on the sodium borohydride reductions of cyclohexanones with polar substituents at the 4 position, for example, adequately explains the observed increases in percent cis alcohol and in the relative rate for reduction. Association of the polar Z group with the metal ion complexed carbonyl group (structure 6) stabilizes the transition state for hydride transfer and, at the same time, effectively blocks hydride attack from the direction that would lead to the less stable trans alcohol. Indeed, results such as



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these suggest a corollary to the principle of complexation-induced conformational perturbation: that the *conformation of the reacting ketone in the transition state for hydride transfer is altered by remote polar substituents in order to maximize stabilization of the complexed carbonyl group and minimize interference between the complexing agent and substituent groups on α positions.*[30]

It must be emphasized that those same factors that influence conformational equilibration and the rates for conformational interchange[15,26,27] are integrated in the principle of complexation-induced conformational perturbation. Theories of stereoselectivity that are based on conformational rigidity present an unwarranted oversimplification of energy minimization in the transition state for nucleophilic addition reactions. Complexation with the carbonyl group modifies the conformation of the reacting ketone. Only conformationally rigid ketones such as norcamphor can be expected to be relatively insensitive to the complexing agent. The stereochemical course in nucleophilic additions to flexible ketones, particularly cyclohexanones, is demonstrably affected by both the complexing agent and the nucleophile. In our survey of nucleophilic addition reactions with cyclic ketones we have found no stereochemical results that could not be explained by application of the principle of complexation-induced conformational perturbation.[31,32] We expect that this same principle can also be applied to nucleophilic additions to acyclic ketones and, with suitable modifications, can be used to explain the stereochemical course of other stereoselective processes.[35]

Experimental Section

Methods and Materials. Instrumentation has been previously described.[6d] The Varian Model 485 digital integrator and the Varian CDS 101 data system were used to determine peak areas in GLC analyses. Commercial samples of 3- and 4-methylcyclohexanones and of *trans*-1-decalone were used without further purification. 2-Methylcyclohexanone and 4-*tert*-butylcyclohexanone were purified by distillation prior to use. 3,3,5-Trimethylcyclohexanone was prepared by a standard Jones oxidation procedure from commercially available 3,3,5-trimethylcyclohexanol; 2-decalol was similarly oxidized to 2-decalone. Isomeric alcohol mixtures were either commercially available or were prepared from the corresponding ketones by lithium aluminum hydride reduction. Diethyl- and triethylsilane were commerically available and were used without further purification. *n*-Butylsilane was prepared by lithium aluminum hydride reduction of *n*-butyltrichlorosilane.[36] Commercial boron trifluoride etherate was purified by distillation from calcium hydride through a 10-cm Vigreux column under a slow flow of nitrogen and was stored over calcium hydride and under nitrogen in a refrigerator at 5 °C.

***cis*-4-*tert*-Butyl-2-methylcyclohexanone.** A solution of 32.9 g of 4-*tert*-butyl-2-methylphenol in 175 mL of glacial acetic acid was hydrogenated at room temperature and 45 psi of initial pressure according to the procedure of Allinger and co-workers,[37] using 1.0 g of platinum oxide. The resulting 4-*tert*-butyl-2-methylcyclohexanol, which was isolated in 80% yield, was then oxidized by chromic acid in aqueous acetone to *cis*-4-*tert*-butyl-2-methylcyclohexanone in 75% yield by the procedure of Djerassi et al.,[38] with the workup procedure similar to that used in standard Jones oxidation procedures. The resulting dark orange solution was distilled to give a clear, colorless liquid, bp 82–84 °C (1.1 Torr) [lit.[39] 110–113 °C (14 Torr)]. The isolated ketone was free of alcohol and isomerically pure by ^{1}H NMR[37,40] and GLC analysis (6 ft 10% DEGS on Chromosorb W).

General Organosilane Reduction Procedure in Boron Trifluoride Etherate. Boron trifluoride etherate (5.0 mmol) was added dropwise by syringe to an ice-bath cooled and rapidly stirred solution of the ketone (5.0 mmol) and organosilane (5.5 mmol) that were contained in a round-bottom flask fitted with a gas inlet tube, septum, and drying tube. The reaction system was flushed with dry nitrogen or argon prior to the addition of BF_3·Et_2O. After the addition was complete the homogeneous solution was allowed to warm to room temperature. Generally a white precipitate formed as the reaction progressed. Although reaction times for >95% reduction were less than 1 h, the reaction was allowed to continue for 24 h. An excess of 3 N sodium hydroxide was then slowly added to the reaction mixture and stirring was continued for an additional 30 min. The hydrolyzed mixture was then extracted three times with ether, the combined ether extract was passed through anhydrous magnesium sulfate, and the magnesium sulfate filter cake was rinsed several times with small portions of ether. The combined ether washes and extract was concentrated under reduced pressure, and the products were subjected to GLC analyses. Yields of recovered alcohol products, determined by GLC analyses through reference to an internal standard and corrected for detector response, were 65–82%. Aldol condensation competes with reduction in reactions that employ BF_3·Et_2O.[1]

Effect of BF_3·Et_2O Concentration on Stereoselectivity. Since BF_3·Et_2O is a reactant in the reductive conversion of ketones to borate esters,[1] stereoselectivity in reductions of alkyl-substituted cyclohexanones may be expected to be sensitive to the boron trifluoride to ketone ratio. Organosilane reductions of 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, *trans*-1-decalone, and *cis*-4-*tert*-butyl-2-methylcyclohexanone were, therefore, performed at two different molar ratios of boron trifluoride to ketone. The results from reductions of these ketones using a molar ratio of BF_3:ketone of 1.0 were given in Tables I–V. Reductions using a molar ratio of BF_3:ketone equal to 0.38 were performed in the manner previously described. Reaction times for complete reduction were generally 24 h. Alcohol products were obtained in 84–89% isolated yield. Stereoselectivities in the formation of the less stable alcohol isomer from reductions of 4-*tert*-butylcyclohexanone, *trans*-1-decalone, and *cis*-4-*tert*-butyl-2-methylcyclohexanone by *n*-butylsilane, diethylsilane, and triethylsilane with a BF_3:ketone molar ratio of 0.38, and from the reduction of 2-methylcyclohexanone by triethylsilane under the same conditions, were 1–3% less than those from reductions with a BF_3:ketone molar ratio of 1.0. For reductions of 2-methylcyclohexanone with *n*-butylsilane and diethylsilane using a BF_3:ketone molar ratio of 0.38, the percent yield of *cis*-2-methylcyclohexanol was 2% greater than in reductions using a BF_3:ketone molar ratio of 1.0. Thus, the variations in stereoselectivity by changing the BF_3·Et_2O concentration are not large, particularly when compared to those observed in sodium borohydride reductions,[10a] and the results obtained for organosilane reductions using 1:1 BF_3:Et_2O accurately reflect the effect of boron trifluoride complexation with alkyl-substituted cyclohexanones.

Other Reduction Procedures. Organosilane reductions in trifluoroacetic acid were performed as previously described.[6d] Sodium borohydride reductions in isopropyl alcohol were performed according to the procedure of Wigfield and Phelps[6b,c,41] with a twofold molar excess of sodium borohydride over ketone. Reductions by lithium aluminum hydride were run in anhydrous ethyl ether using equimolar amounts of $LiAlH_4$ and ketone. Control experiments that were run for procedural comparison with published results duplicated literature values for stereoselectivities in reduction.

Product Analyses. Product yields were determined by GLC analyses. Isomeric alcohols from 3- and 4-methylcyclohexanone and from *trans*-1-decalone reductions were separated and analyzed on 6-ft, 10% DEGS columns at 75 °C (3- and 4-methylcyclohexanone reductions) and 110 °C (*trans*-2-decalone reductions). Isomeric alcohols from reductions of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone were separated and analyzed on 7-ft 20% Carbowax 20M columns operated at 170 and 165 °C, respectively. Isomeric alcohols from reductions of *trans*-2-decalone were analyzed on 9-ft 20% Carbowax 20M columns. Isomeric alcohols from reductions of *cis*-4-*tert*-butyl-2-methylcyclohexanone were analyzed on 6-ft 10% DEGS columns operated at 120 °C and on 7-ft 20% Carbowax 20M columns operated at 170 °C. In each separation the axial alcohol isomer was eluted first.[6d] The thermal conductivities of the geometrical isomers of each alcohol were assumed to be identical.[42]

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Registry No.—*trans*-2-Decalone, 16021-08-2; *cis*-4-*tert*-butyl-

2-methylcyclohexanone, 3211-27-6; 4-*tert*-butyl-2-methylphenol, 98-27-1; 4-*tert*-butyl-2-methylcyclohexanol, 2484-73-3.

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The Solvatochromic Comparison Method. 5. Spectral Effects and Relative Strengths of the First and Second Hydrogen Bonds by 4-Nitroaniline to Hydrogen Bond Acceptor Solvents[1]

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The enhanced bathochromic shifts attributable to type B hydrogen bonding by 4-nitroaniline (1) to HBA (hydrogen bond acceptor) solvents are more than twice as large as comparable solvatochromic displacements for *N*-methyl-, *N*-ethyl-, and *N*-isopropyl-4-nitroaniline (**2a–c**). Solvatochromic dilution experiments show the VF_{50} values in Me_2SO/CCl_4 (volume fractions of HBA solvent at which the hydrogen bonded complex is half dissociated) to be 0.0057 for **2b** and 0.0063 for **1**. It is concluded that the ratio of the spectral effects of the first and second hydrogen bonds of **1** is $1/(0.93 \pm 0.13)$, whereas hydrogen bond strengths are in a ratio of about 1.5:1.

In part 1 of this series,[3] we reported the solvatochromic comparison of UV-visible spectral data for 4-nitroaniline (**1**) with results in corresponding non-hydrogen-bonding, hydrogen bond acceptor, and amphiprotic solvents for *N,N*-diethyl-4-nitroaniline (**3**). The work was an extension and refinement of an earlier study,[4] in which spectral data for **1** and its *N*-ethyl and *N,N*-diethyl derivatives, in alcohol solvents only, had been correlated through a preliminary, cruder version of the solvatochromic comparison method.[5] In the present paper we extend our investigations to *N*-methyl- (**2a**), *N*-ethyl- (**2b**), and *N*-isopropyl-4-nitroaniline (**2c**), and consider how the enhanced solvatochromic shifts attributable to type B hydrogen bonding[6] by these solutes to HBA (hydrogen bond acceptor) solvents,[7] $-\Delta\Delta\nu(\mathbf{2a,b,c}\text{–}\mathbf{3})^{B}_{\leftarrow HRN}$,[8] relate to corresponding $-\Delta\Delta\nu(\mathbf{1}\text{–}\mathbf{3})^{B}_{\leftarrow H_2N}$ displacements determined earlier.[3] We also employ the solvatochromic dilution procedure, described in part 4,[1] to determine relative HBD (hydrogen bond donor)[7] acidities of these indicator solutes.

The purposes of this exercise are to compare the strengths and spectral effects of one hydrogen bond each by the amine protons of **2a–c** to HBA solvents with the strengths and effects of two such hydrogen bonds (presumed) in the case of **1**. The investigation was prompted by findings from the initial study,[4] which appeared to indicate that two type B hydrogen bonds by the amine protons of **1** to alcohol solvents produce more than twice as large an enhanced bathochromic effect as the single type B hydrogen bond formed by **2b**. We considered that this result required corroboration, since a logical (but difficult to accept) corollary seemed to be that the second hydrogen bond by **1** to HBA solvents is as strong as (or stronger than) the first.

In HBD solvents, **3** has been shown to behave as a weak type A hydrogen bond[6] acceptor at the nitro oxygens;[9] **1** and **2a–c** most likely behave similarly, and spectral effects of type A bonding to nitro are assumed to cancel out in the solvatochromic correlation equations.[10] In HBA solvents **1** and **2a–c**, but not **3**, can act as type B hydrogen bond donors at the amine substituents; hence, the differential solvatochromic shifts between **1**, **2a–c**, and **3** are considered to reflect the spectral effects of hydrogen bonding by the amine protons. Since such type B bonding leads to greater stabilization (hydrogen bond strengthening) in electronic excited states relative to ground states of $[RHN^{+}{=}C(1) \rightarrow C(4){=}NO_2^{-}]$ electronic transitions, spectral displacements due to such solvent association are bathochromic, with the effects increasing with increasing β values (indicators of HBA basicity)[3] of the solvents.

In the documentation of solvent hydrogen bonding effects on electronic spectra by the solvatochromic comparison method, the first step involves the determination of relative solvent polarity effects by linear correlation of positions of absorption maxima of the HBD indicator solute (**2a–c** in the present instance) with those of the non-HBD reference solute (**3**) in a series of non-HBA solvents. Spectral data required for these correlations are assembled in Table I, and $\nu(\mathbf{2b})_{max}$ values are plotted against corresponding $\nu(\mathbf{3})_{max}$ values in Figure 1.

It is seen in the plot, and confirmed by least-squares regression analyses, that the linear correlations of the data in the non-HBA solvents (the first nine solvents in Table I) are excellent. The regression equations are

$$\nu(\mathbf{2a})_{max} = 1.1031\ \nu(\mathbf{3})_{max} - 0.943\ \text{kK} \qquad (1a)$$

with r (the correlation coefficient) = 0.996 and SD (the standard deviation) = 0.11 kK,

$$\nu(\mathbf{2b})_{max} = 1.0834\ \nu(\mathbf{3})_{max} - 0.589\ \text{kK} \qquad (1b)$$

with r = 0.997 and SD = 0.10 kK, and

$$\nu(\mathbf{2c})_{max} = 1.0460\ \nu(\mathbf{3})_{max} + 0.232\ \text{kK} \qquad (1c)$$

with r = 0.997 and SD = 0.09 kK. These standard deviation values represent about the best precision which might be expected in the light of the band overlap and band dissymmetry effects which are usually encountered in electronic spectra of this type, coupled with the experimental uncertainties in picking the exact positions of maxima of relatively broad bands.[11]

As the next step in the solvatochromic comparisons, the enhanced bathochromic shifts resulting from type B hydrogen bonding by the HBD solutes are evaluated by substracting observed ν_{max} values for **2a–c** in HBA and amphiprotic solvents from values calculated through eq 1a–c and the corresponding $\nu(\mathbf{3})_{max}$ results.

$$-\Delta\Delta\nu(\mathbf{2a,b,c}\text{–}\mathbf{3})^{B}_{\leftarrow HRN} = \nu(\mathbf{2a,b,c})^{calcd}_{eq\ 1a\text{–}c} - \nu(\mathbf{2a,b,c})^{obsd}_{max} \qquad (2)$$

Equation 2 cancels out solvent polarity effects as well as effects deriving from type A bonding[6] by the amphiprotic solvents to nitro oxygens (assumed to be similar for **2a–c** and **3**). Values of $\nu(\mathbf{2a,b,c})^{calcd}_{eq\ 1a\text{–}c}$ and $-\Delta\Delta\nu(\mathbf{2a,b,c}\text{–}\mathbf{3})$, as well as averaged $-\Delta\Delta\nu(\mathbf{2}\text{–}\mathbf{3})$ values are included in Table I, together with $-\Delta\Delta\nu(\mathbf{1}\text{–}\mathbf{3})^{B}_{\leftarrow H_2N}$ terms reported earlier.[3] It is seen that for most solvents considered the $-\Delta\Delta\nu(\mathbf{1}\text{–}\mathbf{3})$ terms are more than twice as large as the corresponding $-\Delta\Delta\nu(\mathbf{2}\text{–}\mathbf{3})$ terms. Also, for solvents with major steric requirements about the HBA site (e.g., **46, 48, 49, 101**) there does seem to be steric weakening of the hydrogen bonding effect, particularly in the case of the *N*-isopropyl indicator compound.

To complete these solvatochromic comparisons, it remains to be shown that the enhanced solvatochromic shifts are

Table I. Solvatochromic Comparison of Spectral Data for *N*-Methyl- (2a), *N*-Ethyl- (2b), and *N*-Isopropyl-4-nitroaniline (2c) with Results in Corresponding Solvents for *N,N*-Diethyl-4-nitroaniline (3)

Solvent[c]	β_{1-8}[a]	ν(3)	ν(2a) Obsd	ν(2a) Calcd	$-\Delta\Delta\nu$ (2a−3)	ν(2b) Obsd	ν(2b) Calcd	$-\Delta\Delta\nu$ (2b−3)	ν(2c) Obsd	ν(2c) Calcd	$-\Delta\Delta\nu$ (2c−3)	$-\Delta\Delta\nu$ (2−3) av	$-\Delta\Delta\nu$ (1−3)
1. Hexane		27.71	29.50			29.33			29.15				
2. Cyclohexane		27.40	29.37			29.15			28.90				
6. CCl_4		26.70	28.57			28.37			28.17				
8. Toluene		25.87	27.55			27.47			27.36				
10. $Cl_2C{=}CCl_2$		25.76	27.59			27.40			27.25				
14. Benzene		25.60	27.36			27.25			27.14				
15. Chlorobenzene		25.38	26.92			26.77			26.67				
20. Ethylene dichloride		25.06	26.60			26.46			26.32				
21. Methylene chloride		24.96	26.67			26.49			26.35				
17. Anisole	0.247	25.31	26.67	26.97	0.30	26.56	26.83	0.27	26.46	26.71	0.25	0.27	0.67
39. Ethyl chloroacetate	0.363	25.28	26.39	26.94	0.55	26.28	26.80	0.52	26.18	26.67	0.49	0.52	0.91
9. Dioxane	0.379	25.77	26.92	27.48	0.56	26.77	27.33	0.56	26.56	27.19	0.63	0.58	1.06
46. Dibenzyl ether[b]	0.410	25.09	26.35	26.73	0.38	26.18	26.59	0.41	26.28	26.48	0.20	0.39	1.14
47. Ethyl benzoate	0.431	25.31	26.39	26.97	0.58				26.14	26.71	0.57	0.58	1.22
7. Ethyl ether	0.488	26.52	27.66	28.31	0.65	27.55	28.14	0.59	27.36	27.97	0.61	0.62	1.44
5. Butyl ether	0.490	26.85	27.82	28.68	0.86	27.78	28.50	0.72	27.59	28.32	0.73	0.77	1.40
11. Ethyl acetate	0.474	25.74	26.81	27.45	0.64	26.77	27.30	0.53	26.60	27.16	0.56	0.58	1.35
18. Acetone	0.499	25.22	26.28	26.88	0.60	26.18	26.73	0.55	26.01	26.61	0.60	0.58	1.42
16. 2-Butanone	0.504	25.28	26.32	26.94	0.62	26.18	26.80	0.62	26.08	26.67	0.59	0.61	1.44
40. Tetrahydropyran	0.512	25.74	26.77	27.45	0.68	26.67	27.30	0.53	26.53	27.16	0.63	0.61	1.46
13. Tetrahydrofuran	0.556	25.61	26.60	27.31	0.71	26.46	27.16	0.70	26.35	27.02	0.67	0.69	1.55
27. Butyrolactone	0.497	24.60	25.64	26.19	0.55	25.54	27.06	0.52	25.45	25.96	0.51	0.53	1.29
48. Tri-*n*-butylamine	0.635	27.14	28.05	29.00	0.95	28.09	28.81	0.72	28.05	28.62	0.57[b]	0.84	1.87
49. Dimethylbenzylamine	0.595	26.04	26.74	27.78	1.04	26.70	27.62	0.92	26.70	27.47	0.77	0.91	1.66
24. Pyridine	0.661	24.78	25.48	26.39	0.91	25.38	26.26	0.88	25.35	26.15	0.80	0.86	1.87
25. Dimethylformamide	0.690	24.66	25.45	26.26	0.81	25.35	26.13	0.78	25.19	26.03	0.84	0.81	1.98
29. Dimethyl sulfoxide	0.749	24.30	25.06	25.86	0.80	24.91	25.74	0.83	24.81	25.65	0.84	0.82	2.08
19. Triethyl phosphate	0.772	25.19	25.87	26.84	0.97	25.77	26.70	0.93	25.61	26.58	0.97	0.96	2.22
26. Hexamethylphosphoramide	0.990	24.75	25.25	26.36	1.11	25.06	26.22	1.18	25.06	26.12	1.06	1.12	2.80
23. Dimethylacetamide	0.749	24.75	25.45	26.36	0.91	25.35	26.22	0.87	25.25	26.12	0.87	0.88	2.05
28. *N*-Methylpyrrolidone	0.741	24.60	25.32	26.19	0.87	25.22	26.06	0.84	25.09	25.96	0.87	0.86	2.09
51. Cyclopentanone	0.537	25.09	26.11	26.73	0.62	25.97	26.59	0.62	25.84	26.48	0.64	0.63	1.51
101. *tert*-Butyl alcohol	1.014	25.61	25.81	27.32	1.50	25.77	27.17	1.40	25.84	27.02	1.16	1.35	2.66
102. 2-Propanol	0.949	25.51	25.94	27.20	1.26	25.84	27.05	1.21	25.64	26.91	1.27	1.25	2.58
103. 1-Butanol	0.884	25.51	25.87	27.20	1.33	25.87	27.05	1.18	25.71	26.91	1.20	1.24	2.37
112. 1-Propanol	0.746	25.35	25.91	27.02	1.11	25.81	26.87	1.06	25.64	26.75	1.09	1.09	2.10
104. Ethanol	0.773	25.48	26.11	27.16	1.05	25.94	27.02	1.08	25.77	26.88	1.11	1.08	2.16
105. Methanol	0.615	25.16	26.08	26.81	0.73	25.87	26.67	0.80	25.71	26.55	0.84	0.79	1.73
106. 2-Phenylethanol	0.640	24.94	25.67	26.57	0.90	25.45	26.43	0.98	25.25	26.32	1.07	0.98	1.78
107. Ethylene glycol	0.522	24.10	25.13	25.64	0.51	25.09	25.52	0.43	24.97	25.44	0.47	0.47	1.44
109. Benzyl alcohol	0.498	24.33	25.25	25.90	0.65	25.19	27.77	0.58	25.13	25.68	0.55	0.59	1.57
111. Water	0.181	23.23	24.60	24.68	0.08	24.45	24.58	0.13	24.33	24.53	0.20	0.14	0.40
113. Trifluoroethanol	Nil	23.70	25.19	25.20	0.01	25.06	25.07	0.01	24.91	25.02	0.11	0.05	Nil

[a] Reference 3. [b] Large steric effect; excluded from correlation. [c] Solvent numbering is the same in all papers of this series.

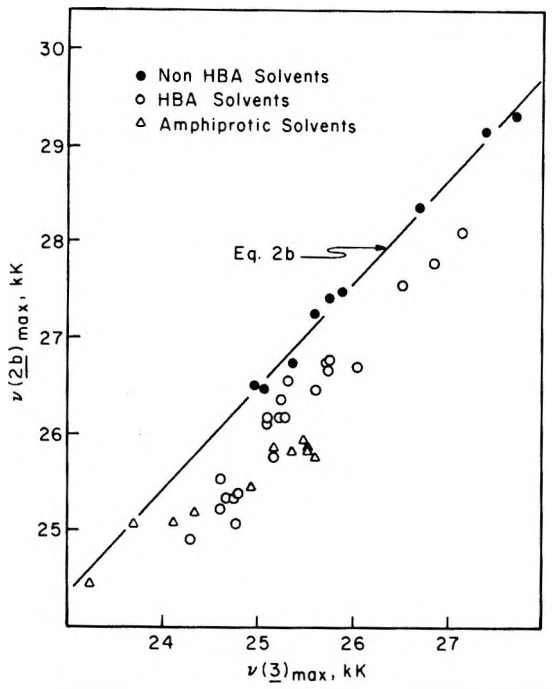


Figure 1. Plot of ν_{max} values for *N*-ethyl-4-nitroaniline (**2b**) against results in corresponding solvents for *N,N*-diethyl-4-nitroaniline (**3**).

consistent with the chemistry involved and (in the present case of type B hydrogen bonding) reflect a reasonable order of solvent HBA strengths. This is demonstrated by good linear plots of $-\Delta\Delta\nu$(**2a,b,c–3**) terms vs. solvent β_{1-8} values,[3,12] and by statistically satisfactory least-squares correlations. The plots are shown in Figure 2; the regression equations are

$$-\Delta\Delta\nu(\mathbf{2a–3})^{B}_{\leftarrow HRN} = 1.350\beta_{1-8} - 0.023 \text{ kK} \quad (3a)$$

with n = 33 (22 HBA, 11 amphiprotic solvents), r = 0.937, and SD = 0.11 kK,

$$-\Delta\Delta\nu(\mathbf{2b–3})^{B}_{\leftarrow HRN} = 1.327\beta_{1-8} - 0.050 \text{ kK} \quad (3b)$$

with n = 32, r = 0.954, and SD = 0.10 kK,

$$-\Delta\Delta\nu(\mathbf{2c–3})^{B}_{\leftarrow HRN} = 1.208\beta_{1-8} + 0.033 \text{ kK} \quad (3c)$$

with n = 32, r = 0.938, and SD = 0.09 kK, and

$$-\Delta\Delta\nu(\mathbf{2}_{av}\mathbf{–3})^{B}_{\leftarrow HRN} = 1.281\beta_{1-8} - 0.007 \text{ kK} \quad (3d)$$

with n = 33, r = 0.952, and SD = 0.09 kK. For comparison, the corresponding regression equation for 4-nitroaniline is

$$-\Delta\Delta\nu(\mathbf{1–3})^{B}_{\leftarrow H_2N} = 2.755\beta_{1-8} + 0.026 \text{ kK} \quad (4)$$

with r = 0.994 and SD = 0.07 kK.[13]

Particularly to be noted in eq 3a–d are the low values of the intercepts compared with the SD's, as well as the fact that the latter are not larger than the SD's of antecedent eq 1a–c. These results lend confidence that the correlations do indeed reflect direct proportionality of the $-\Delta\Delta\nu$ with the β_{1-8} terms, and that we do no violence to the data in force-fitting the regression lines through the origins. On this basis, the correlation equations become

$$-\Delta\Delta\nu(\mathbf{2a–3})^{B}_{\leftarrow HRN} = 1.312\beta_{1-8} \pm 0.085 \text{ kK} \quad (5a)$$

$$-\Delta\Delta\nu(\mathbf{2b–3})^{B}_{\leftarrow HRN} = 1.240\beta_{1-8} \pm 0.088 \text{ kK} \quad (5b)$$

$$-\Delta\Delta\nu(\mathbf{2c–3})^{B}_{\leftarrow HRN} = 1.260\beta_{1-8} \pm 0.093 \text{ kK} \quad (5c)$$

$$-\Delta\Delta\nu(\mathbf{2}_{av}\mathbf{–3})^{B}_{\leftarrow HRN} = 1.281\beta_{1-8} \pm 0.090 \text{ kK} \quad (5d)$$

and, for comparison,

$$-\Delta\Delta\nu(\mathbf{1–3})^{B}_{\leftarrow H_2N} = 2.793\beta_{1-8} \pm 0.051 \text{ kK} \quad (6)$$

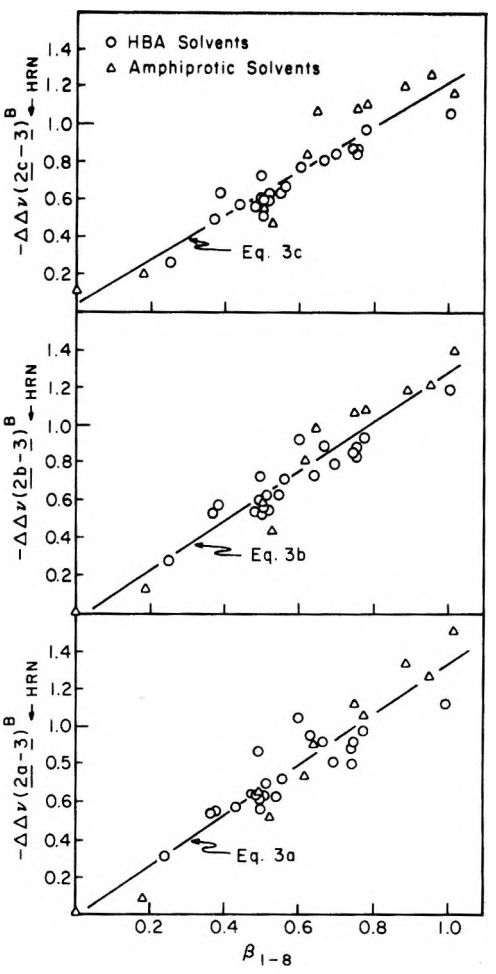


Figure 2. Enhanced bathochromic shifts attributable to hydrogen bonding by *N*-methyl-, *N*-ethyl-, and *N*-isopropyl-4-nitroaniline (**2a–c**) to HBA solvents plotted against solvent β values.

The proportionality constants in eq 5a–d and 6, which we shall refer to as b values,[14] can now serve us as average relative measures of the bathochromic effects of type B hydrogen bonding on electronic spectra of **1** and **2a–c**. Plots of $-\Delta\Delta\nu(\mathbf{2}_{av}\mathbf{–3})$ and $-\Delta\Delta\nu$(**1–3**) vs. β_{1-8}, with the regression lines force-fitted through the origins (slopes = b), are compared in Figure 3.

Solvatochromic Comparisons of Spectra for 3-Methyl-4-nitroaniline Derivatives. Although the $-\Delta\Delta\nu$ and b values for **2a–c** seemed straightforward, unambiguous, and mutually supporting,[15] we were uncomfortable that the $-\Delta\Delta\nu$(**1–3**) values with which they were compared involved only single HBD and non-HBD indicator solutes. It seemed desirable to narrow the possibility that the more than doubled b value for **1** relative to **2a–c** might derive from some unconsidered obscure effect, specific to either **1** or **3**. Toward this end, we include here the results of exactly analogous solvatochromic comparisons of spectral data for 3-methyl-4-nitroaniline (**4**) and *N*-ethyl-3-methyl-4-nitroaniline (**5**), with the reference indicator *N,N*-diethyl-3-methyl-4-nitroaniline (**6**).[16] Spectral data and derived $-\Delta\Delta\nu$ values are assembled in Table II.

As before, the results in the non-hydrogen-bonding solvents are nicely linear with one another. The regression equations are

$$\nu(\mathbf{4})_{max} = 1.1163\nu(\mathbf{6})_{max} + 0.539 \text{ kK} \quad (7)$$

with n = 9, r = 0.998, and SD = 0.09 kK, and

$$\nu(\mathbf{5})_{max} = 1.1054\nu(\mathbf{6})_{max} - 1.209 \text{ kK} \quad (8)$$

Table II. Solvatochromic Comparison of Spectral Data for 3-Methyl-4-nitroaniline (4) and *N*-Ethyl-3-methyl-4-nitroaniline (5) with Results in Corresponding Solvents for *N,N*-Diethyl-3-methyl-4-nitroaniline (6)

Solvent	ν(6)	ν(4) Obsd	ν(4) Calcd	$-\Delta\Delta\nu$ (4–6)	ν(5) Obsd	ν(5) Calcd	$-\Delta\Delta\nu$ (5–6)
1. Heptane	27.78	31.55			29.50		
2. Cyclohexane	27.62	31.35			29.28		
43. $Cl_2C{=}CCl_2$	26.88	30.53			28.53		
6. CCl_4	26.85	30.58			28.53		
12. 1,1,1-Trichloroethane	26.11				27.62		
10. $Cl_2C{=}CHCl$	26.01	29.54			27.55		
30. Chloroform	25.22	28.82			26.74		
20. $ClCH_2CH_2Cl$	25.25	28.57			26.63		
21. Methylene chloride	25.19	28.74			26.67		
22. $ClCH_2CHCl_2$	25.19	28.61			26.60		
17. Anisole	25.61	28.49	29.13	0.64	26.77	27.10	0.33
39. Ethyl chloroacetate	25.38	27.82	28.87	1.05	26.42	26.86	0.43
9. Dioxane	25.94	28.37	29.50	1.13	27.03	27.47	0.44
46. Dibenzyl ether	25.41	28.01	28.90	0.89	26.49	26.88	0.39
47. Ethyl benzoate	25.48	27.89	28.98	1.09	26.56	26.96	0.40
11. Ethyl acetate	26.01	28.13	29.67	1.54	26.92	27.54	0.62
7. Ethyl ether	26.70	28.78	30.34	1.56	27.62	28.31	0.69
5. Butyl ether	27.03	29.15	30.71	1.56	27.97	28.67	0.70
27. Butyrolactone	24.84	27.03	28.27	1.24	25.81	26.25	0.44
18. Acetone	24.41	27.47	28.90	1.43	26.32	28.88	0.56
16. 2-Butanone	25.54	27.59	29.05	1.46	26.46	27.02	0.56
40. Tetrahydropyran	26.08	27.97	29.65	1.68	26.85	27.62	0.77
51. Cyclopentanone	25.38	27.40	28.87	1.47	26.28	26.85	0.57
13. Tetrahydrofuran	25.91	27.86	29.46	1.60	26.74	27.43	0.69
49. Dimethylbenzylamine	26.32	28.13	29.92	1.79	27.03	27.89	0.86
48. Tri-*n*-butylamine	27.32	29.50	31.04	1.54	28.25	28.99	0.74
24. Pyridine	24.97	26.74	28.41	1.67	25.64	26.39	0.75
25. Dimethylformamide	24.91	26.46	28.35	1.89	25.58	26.33	0.75
28. *N*-Methylpyrrolidone	24.81	26.18	28.23	2.05	25.45	26.22	0.77
29. Dimethyl sulfoxide	24.60	26.04	28.00	1.96	25.25	25.98	0.73
23. Dimethylacetamide	24.97	26.32	28.41	2.09	25.58	26.39	0.81
19. Triethyl phosphate	25.38	26.67	28.87	2.20	25.97	26.85	0.88
26. Hexamethylphosphoramide	25.00	25.67	28.45	2.78	25.28	26.43	1.15
101. *tert*-Butyl alcohol	25.74	26.60	29.27	2.67	25.94	27.24	1.30
102. 2-Propanol	25.54	26.63	29.05	2.42	25.87	27.02	1.15
103. 1-Butanol	25.41	26.70	28.90	2.20	25.87	26.88	1.01
112. 1-Propanol	25.41	26.63	28.90	2.27	25.81	26.88	1.07
104. Ethanol	25.51	26.88	29.02	2.14	26.04	26.99	0.95
105. Methanol	25.22	26.95	28.69	1.74	25.91	26.67	0.76
107. Ethylene glycol	24.51	26.35	27.90	1.55	25.03	25.88	0.85
109. Benzyl alcohol	24.57	26.63	27.97	1.34	25.28	25.95	0.67
106. 2-Phenylethanol	24.84	26.74	28.27	1.53	25.58	26.25	0.67
111. Water	23.59	26.52	26.87	0.35	24.75	24.86	0.11
113. Trifluoroethanol	23.87	27.28	27.19	−0.09	25.19	25.18	−0.01

with $n = 10$, $r = 0.999$, and SD = 0.05 kK. Also as before, the $-\Delta\Delta\nu$ terms, arrived at by subtracting observed values of $\nu(4)_{max}$ and $\nu(5)_{max}$ from values calculated through eq 7 and 8, are nicely linear with β_{1-8} values. These correlation equations are

$$-\Delta\Delta\nu(4\text{–}6)^{B}_{\leftarrow H_2N} = 2.667\beta_{1-8} + 0.043 \text{ kK} \quad (9)$$

with $n = 34$ (23 HBA, 11 amphiprotic solvents), $r = 0.971$, and SD = 0.15 kK, and

$$-\Delta\Delta\nu(5\text{–}6)^{B}_{\leftarrow HRN} = 1.200\beta_{1-8} - 0.005 \text{ kK} \quad (10)$$

with $n = 34$, $r = 0.938$, and SD = 0.10 kK. Again the relatively small values of the intercepts compared with the SD's in eq 9 and 10 warrant force-fitting and regression lines through the origins, whereupon we arrive at the proportionalities with β_{1-8},

$$-\Delta\Delta\nu(4\text{–}6)^{B}_{\leftarrow H_2N} = 2.740\beta_{1-8} \pm 0.115 \text{ kK} \quad (11)$$

$$-\Delta\Delta\nu(5\text{–}6)^{B}_{\leftarrow HRN} = 1.191\beta_{1-8} \pm 0.085 \text{ kK} \quad (12)$$

Thus, the enhanced solvatochromic effects of hydrogen bonding by the double hydrogen bond donor are again more than twice as large as those for the closely related donor of a single hydrogen bond.

Estimation of Relative HBD Acidities of 1 and 2b by the Solvatochromic Dilution Method. The b values for the indicators, 4-$NO_2C_6H_4N(H)R$, vary with substituent σ^* values as follows: R = CH_3, $\sigma^* = 0.00$, $b = 1.312$; R = CH_3CH_2, $\sigma^* = -0.10$, $b = 1.240$; R = $(CH_3)_2CH$, $\sigma^* = -0.19$, $b = 1.260$. We have arrived at a b value for the first hydrogen bond of 1 by estimating that this progression, in its extension to R = H, $\sigma^* = +0.49$, gives a likeliest value in the range $b = 1.45 \pm 0.10$. Taken with $b = 2.79$ for the combined effects of both hydrogen bonds, it follows that the spectral effect of the second hydrogen bond is between 0.80 and 1.07 times as great as that of the first.

Is it a necessary corollary of the above that the second hydrogen bond by 1 to HBA solvents is about *as strong* as the first? To answer this question, we have used the solvatochromic dilution procedure, described in part 4,[1] to assess relative HBD acidities of 1 and **2b**. This procedure involves determining how $-\Delta\Delta\nu$ values for the complex between the HBD indicator solutes and an HBA solvent vary as the HBA solvent is progressively diluted into a non-HBA cosolvent.

Table III. Solvatochromic Comparison of Spectral Data for 4-Nitroaniline (1) and *N*-Ethyl-4-nitroaniline (2b) with Results for *N,N*-Diethyl-4-nitroaniline (3) in Mixed Dimethyl Sulfoxide–Carbon Tetrachloride Solvents[a]

Vol fraction Me_2SO	$\nu(3)_{max}^{obsd}$	$\nu(1)$ Obsd	$\nu(1)$ Calcd	$-\Delta\Delta\nu$ (1–3)	$\nu(2b)$ Obsd	$\nu(2b)$ Calcd	$-\Delta\Delta\nu$ (2b–3)
1.000	24.27	25.74	27.76	2.02	24.88	25.71	0.83
0.800	24.39	25.81	27.88	2.07	24.94	25.84	0.90
0.600	24.60	25.87	28.10	2.23	25.06	26.06	1.00
0.400	24.84	26.08	28.35	2.27	25.25	26.32	1.07
0.200	25.19	26.25	28.71	2.46	25.51	26.70	1.19
0.100	25.58	26.56	29.11	2.55	25.74	27.12	1.38
0.080	25.67	26.70	29.21	2.51	25.88	27.22	1.34
0.060	25.84	26.95	29.38	2.43	25.97	27.41	1.44
0.040	26.04	27.21	29.59	2.38	26.21	27.62	1.41
0.020	26.32	27.86	29.88	2.02	26.60	27.93	1.33
0.010	26.46	28.37	30.02	1.65	27.14	28.08	0.94
0.008	26.49	28.57	30.10	1.57	27.21	28.11	0.90
0.006	26.56	28.94	30.13	1.19	27.40	28.19	0.79
0.005	26.56	29.07	30.13	1.06	27.62	28.19	0.57
0.004	26.60	29.24	30.17	0.93	27.78	28.23	0.45
0.003	26.63	29.41	30.20	0.79	27.89	28.27	0.36
0.002	26.67	29.67	30.24	0.57	27.97	28.31	0.34
0.001	26.67	29.94	30.24	0.30	28.15	28.31	0.16
0.000	26.70	30.33	30.27	−0.06	28.37	28.34	−0.03

[a] Data for 1 and 3 differ slightly from results for the same materials reported in part 4.[1] The data were obtained in separate experimental studies on different spectrophotometers. Comparison of the two sets of data allows evaluation of representative experimental precision to be expected in solvatochromic comparisons.

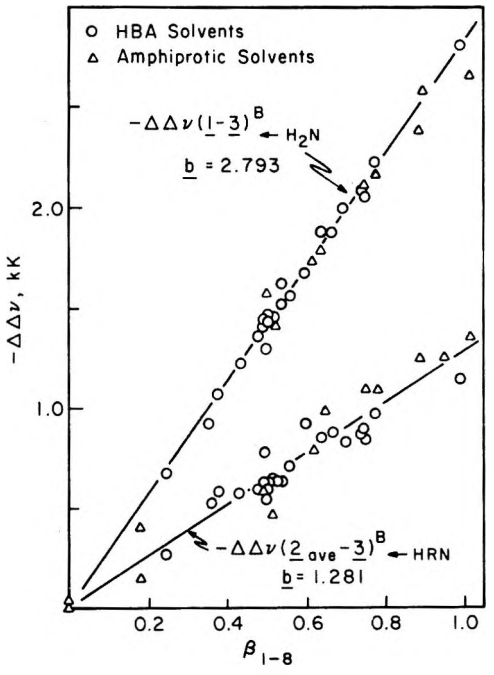


Figure 3. Enhanced bathochromic shifts for 4-nitroaniline and average shifts for the *N*-alkyl-4-nitroanilines plotted against solvent β values.

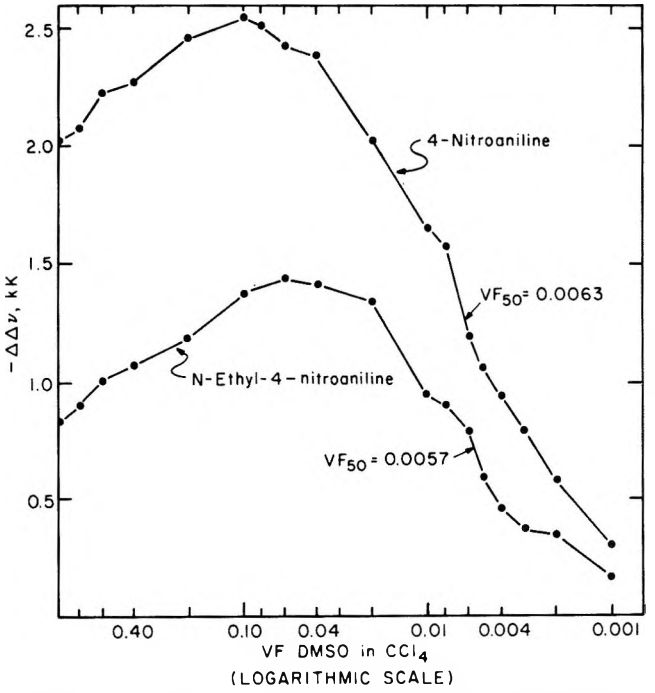


Figure 4. Solvatochromic dilution plots for 4-nitroaniline and *N*-ethyl-4-nitroaniline; HBA solvent, Me_2SO; non-HBA cosolvent, CCl_4; reference indicator, *N,N*-diethyl-4-nitroaniline.

VF_{50} values, the volume fractions (HBA solvent in non-HBA cosolvent) at which the HBD:HBA complex is half dissociated,[17] can be used to arrive at rough estimates of the formation constants.

In the present dilution study, **1** and **2b** are the HBD indicator solutes, **3** the non-HBD reference solute, dimethyl sulfoxide the HBA solvent, and carbon tetrachloride the non-HBA cosolvent. Values of ν_{max} in the mixed solvents, together with the $-\Delta\Delta\nu$ terms (obtained, as before, by subtracting ν_{max}^{obsd} values from values calculated through eq 1b and 2), are assembled in Table III, and $-\Delta\Delta\nu$(1–3) and $-\Delta\Delta\nu$(2b–3) terms are plotted against volume fraction (VF) Me_2SO/CCl_4 (the latter on a logarithmic scale) in Figure 4.

It may be seen in the plot that the solvatochromic dilution of **2b** follows the same pattern shown earlier for **1** and other HBD indicator solutes.[1] As the Me_2SO grows progressively more dilute in CCl_4, the $-\Delta\Delta\nu$(2b–3) term first rises to a maximum because of a polarity augmentation effect in the cybotactic region (see discussion in part 4),[1] then falls off as the **2b**:Me_2SO complex begins to dissociate. The volume fraction at which the **2b**:Me_2SO complex is half dissociated,

VF_{50} = 0.0057, corresponding to 0.081 M Me_2SO in CCl_4. This compares with VF_{50} = 0.0063 (0.0062),[18] corresponding to 0.081 M Me_2SO in CCl_4 for the complex with **1**.

These Me_2SO molarities at half-dissociation allow rough estimates of formation constants, and hence relative hydrogen bond strengths. For the half-dissociated **2b**:Me_2SO complex

$$K_f^{2b} = \frac{(\mathbf{2b}{:}Me_2SO)}{(\mathbf{2b})\,(Me_2SO)} = 1/(Me_2SO) = 12.5\ L\ mol^{-1}$$

For the singly hydrogen bonded Me_2SO complex with **1**

$$K_1 = \frac{(\mathbf{1}{:}Me_2SO)}{(\mathbf{1})\,(Me_2SO)}$$

and for the doubly hydrogen bonded complex

$$K_2 = \frac{(Me_2SO{:}\mathbf{1}{:}Me_2SO)}{(\mathbf{1}{:}Me_2SO)\,(Me_2SO)}$$

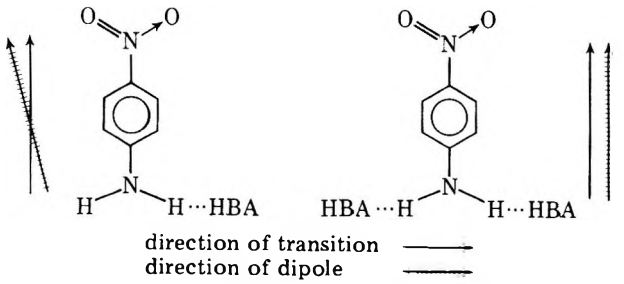
$$K_1K_2 = \frac{(Me_2SO{:}\mathbf{1}{:}Me_2SO)}{(\mathbf{1})\,(Me_2SO)^2}$$

Since, at half-dissociation, (**1**) = (Me_2SO:**1**:Me_2SO)

$$K_1K_2 = 1/(Me_2SO)^2 = 126.2\ L^2\ mol^{-2}$$

If we estimate that the first hydrogen bond by **1** to Me_2SO is about 1.1 times as strong as the **2b**:Me_2SO hydrogen bond, and take into account the statistical factor for the two protons, we arrive at a value of 27.5 L mol^{-1} for K_1 and 4.6 L mol^{-1} for K_2. Again taking into account the statistical factor, it follows that the bond strengths of the first and second type B hydrogen bonds by 4-nitroaniline to HBA solvents are in a ratio of about 13.75/9.2, or about 1.5:1. Thus, the spectral effect of the second compared with the first solvent associated proton is somewhat greater than the relative hydrogen bond strengths would indicate.

We have no easy rationale for this phenomenon. One possible line of reasoning is that optimal solvent stabilization of the excited state of an electronic transition occurs when the direction of that transition corresponds exactly with the direction of the molecule's ground state dipole (a solvent shell best oriented to stabilize the ground state is also optimally oriented for excited state stabilization). Such a situation obtains with uncomplexed **1** and with doubly complexed **1**, but with singly complexed **1** the ground state dipole is rotated



slightly. Hence, in going from **1** to **1**:HBA, we have the bathochromic effect of the hydrogen bonding minus a small Δ term due to noncorrespondence of transition and dipole directions, while on going from **1**:HBA to HBA:**1**:HBA, we have the hydrogen bonding effect *plus* the same small Δ term as the transition and dipole are brought back into line.

The findings reported here are completely consistent with results which we will report in a future paper, wherein substituent, solvent polarity, and solvent hydrogen bonding effects on spectra of 2-, 3-, and 4-nitroanilines will be compared. We will demonstrate that spectral effects and HBD acidities of 3-nitroaniline and *N*-ethyl-3-nitroaniline show about the same relationships to one another as reported here for the 4-nitro derivatives; i.e., for 3-nitroaniline, b = 2.738, VF_{50} (Me_2SO/CCl_4) = 0.0105; for *N*-ethyl-3-nitroaniline, b = 1.485, VF_{50} = 0.0101.

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Registry No.—**1**, 100-01-6; **2a**, 100-15-2; **2b**, 3665-80-3; **2c**, 25186-43-0; **3**, 2216-15-1; **4**, 611-05-2; **5**, 52177-09-0; **6**, 52177-26-1.

References and Notes

(1) Part 4: J. W. Eastes, E. G. Kayser, M. E. Jones, R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.*, submitted for publication.
(2) (a) Naval Surface Weapons Center; (b) University of California; (c) deceased; (d) Visiting Scientist, UCI, 1976–1977.
(3) M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377 (1976).
(4) R. R. Minesinger, E. G. Kayser, and M. J. Kamlet, *J. Org. Chem.*, **36**, 1342 (1971).
(5) In the earlier study,[4] we determined shifts ($-\Delta\nu$ values) from cyclohexane to each solvent for **1**, **2b**, and **3**. The $-\Delta\Delta\nu$ values were simply the differences $[-\Delta\nu(\mathbf{1})] - [-\Delta\nu(\mathbf{3})]$ and $[-\Delta\nu(\mathbf{2b})] - [-\Delta\nu(\mathbf{3})]$. The earlier method is satisfactory where solvent polarity effects are comparable for the indicators being compared, but breaks down where the slopes of the regression lines for the non-hydrogen-bonding solvents differ significantly from unity.
(6) M. J. Kamlet, E. G. Kayser, R. R. Minesinger, M. H. Aldridge, and J. W. Eastes, *J. Org. Chem.*, **36**, 3852 (1971). In type A hydrogen bonding the solvent acts as proton donor and the solute as proton acceptor; the converse applies in type B bonding.
(7) There has been some confusion in the literature as to whether the terms hydrogen bond donor and acceptor refer to the donation and acceptance of the proton or the electron pair. In the present series of papers, HBD (hydrogen bond donor) and HBA (hydrogen bond acceptor) refer to the donation and acceptance of the proton.
(8) The notation $-\Delta\Delta\nu(\mathbf{2a}{-}\mathbf{3})^{B}_{\leftarrow HNR}$ signifies an enhanced bathochromic (or reduced hypsochromic) displacement for **2a** relative to **3**, caused by type B hydrogen bonding by an amine proton to the solvent. See footnote 8 of part 1[3] for an outline of this system, which makes nomenclature much less confusing and cumbersome when several types of hydrogen bonding with concomitant spectral effects occur simultaneously.
(9) M. J. Kamlet, E. G. Kayser, J. W. Eastes, and W. H. Gilligan, *J. Am. Chem. Soc.*, **95**, 5210 (1973).
(10) The possibility of the alcohols acting as hydrogen bond donors and the nitroanilines as hydrogen bond acceptors at the amine nitrogens has been essentially eliminated in the case of sp^2 hybridized 4-nitroaniline derivatives.[6]
(11) To minimize band asymmetry complications (differing band shapes for the same solute in different solvents), we determine ν_{max} by taking the midpoint between the two positions on the spectrum where OD (optical density) = 0.90 OD_{max}.
(12) T. Yokoyama, R. W. Taft, and M. J. Kamlet, *J. Am. Chem. Soc.*, **98**, 3233 (1976). The subscript indicates that data from eight sets of properties were averaged to obtain the β values. As the β scale is used to rationalize hydrogen bonding effects on additional rate constants, equilibrium constants, and spectral and chemical properties, the new experimental information will be used reciprocally to refine and expand the β scale.
(13) No particular significance should be attributed to the very high r value and the low SD for eq 4, since the $-\Delta\Delta\nu(\mathbf{1}{-}\mathbf{3})$ terms were among the properties used in constructing the β scale.
(14) The proportionality constants are the same b terms which we will use in future papers in a generalized equation describing solvent effects on many types of free energy related properties, $XYZ = XYZ_0 + s\pi + a\alpha + b\beta$.
(15) We consider that the difference in b values for **2b** and **2c** is within the range of probable experimental error.
(16) Spectral data for these compounds, as well as for the corresponding 3,5-dimethyl derivatives, were determined as part of a study of the effects of steric inhibition of resonance on type B hydrogen bonding effects. The results of that study will be published in a future paper.
(17) VF_{50} is the volume fraction of HBA solvent in non-HBA cosolvent at which the $-\Delta\Delta\nu$ term is half of the maximum observed value, the latter being equal to the $-\Delta\Delta\nu$ value in the neat HBA solvent plus the cybotactic polarity increment; see part 4.[1]
(18) $-\Delta\Delta\nu$ values and the VF_{50} value differ slightly from those reported earlier, which were determined on a different spectrophotometer. Comparing the data in Table III with results for the same system in Table I of part 4[1] provides a measure of typical experimental reproducibility in solvatochromic dilution studies.

1,2-H Shifts in Carbenes. The Benzonorbornenylidene System[1]

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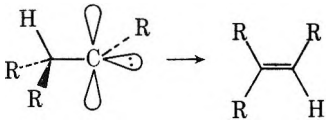
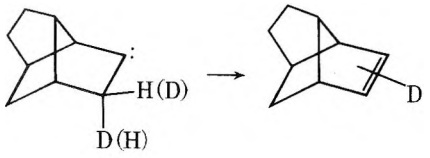
Four carbenes, 1-(*tert*-butyldimethylsiloxy)methyl-2-*exo*- and *endo*-deuterio-5,8-dimethoxybenzonorbornene-3-ylidene (**17b** and **17d**), and 1-(*tert*-butyldimethylsiloxy)methyl-3-*exo*- and -*endo*-deuterio-5,8-dimethoxybenzonorbornene-2-ylidene (**21b** and **21d**), were generated from the corresponding ketones via a thermal Bamford–Stevens route. The exo(x)-H to endo(n)-H migratory ratios were determined to be 13 (for **17**) and 18 (for **21**) at 190 °C. This leads to the activation energy differences $(E_a^n - E_a^x)^{190°C}$ = 2.4–2.7 kcal/mol for the benzonorbornenylidene system.

Alkylcarbenes with an α-CH moiety undergo 1,2-H shifts to form olefins with such facility that it is often difficult to observe intermolecular reactions.[2] This reaction has been the subject of a number of theoretical investigations in recent



years,[3] in which there has been general agreement that the migrating hydrogen proceeds from the conformation shown in **1**, where the empty p orbital and the C–H bond are essentially eclipsed. Calculations show that migration to the full (sp^2) orbital is a considerably higher energy process.[3d]

This question of stereoelectronic control of migration has been considered experimentally with conformationally mobile carbenes,[4] but ideally, a stereochemically well-defined, rigid carbene would be best to test the above theoretical predictions. Such a system was investigated recently by Nickon and his co-workers.[5,6] They found that, in the appropriately deuterium-labeled brexan-5-ylidene (**2**) systems generated from the corresponding sodium tosylhydrazone salts, an exo(x)-H to endo(n)-H migratory ratio of 138 could be derived.[5] Since the ethylene bridge in **2** tends to twist the



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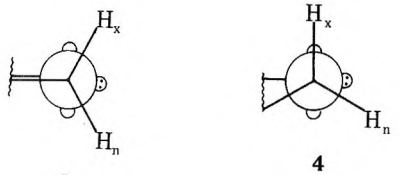


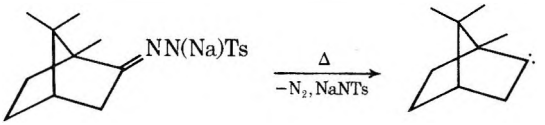
3 **4**

methylene group α to the carbene center away from the conformation shown in **3** and approaching that in **4**, the preference for H_x migration over H_n presumably could be attributed to a stereoelectronic effect, in accord with theoretical calculations.[3] In order to arrive at this conclusion, however, it is necessary to assume that the H_x/H_n migratory ratio is close to unity in an undistorted bicyclo[2.2.1] system.[7]

It is well known that in undistorted bicyclo[2.2.1] carbocations, the H_x/H_n migration ratio is very much larger than unity, although the reasons for this selectivity are not well understood.[8] Since there were no data available in the literature concerning migration tendencies in undistorted [2.2.1] carbenes, we undertook to investigate such a case to ascertain whether or not the above assumption was reasonable.

Results and Discussion

Synthesis. Our choice of substrate (**17** and **21**, Scheme I) was dictated by synthetic and analytical realities, along with a particular property of 2-bicyclo[2.2.1]carbenes. Thus it is well known that 2,3-H migration is not competitive with intramolecular cyclization in carbenes such as **5**.[9a] For this



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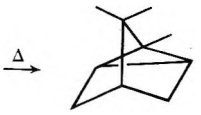
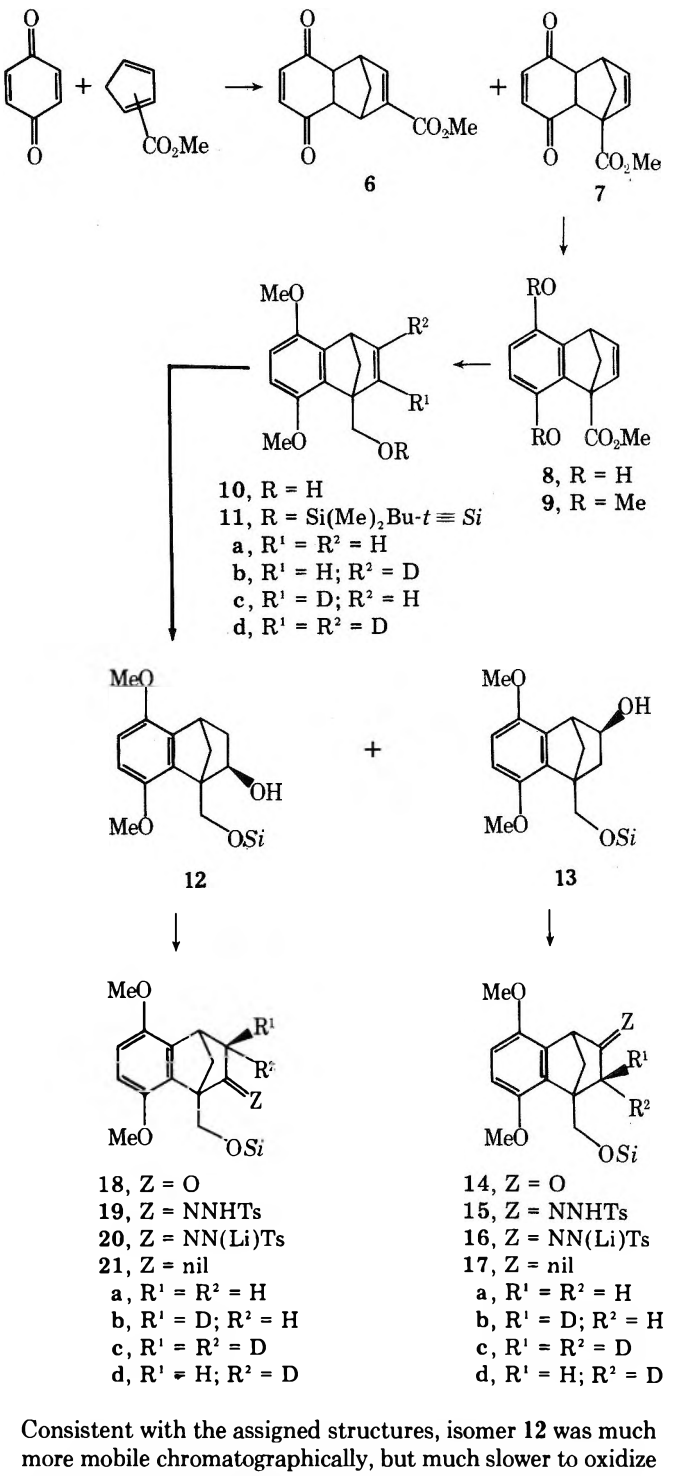


reason, it was necessary to use a substrate which would preclude such a reaction, and we chose a benzo group in the 5,6 position for this purpose.[9b] It was also necessary to have a "marker" on the molecule to identify the migration origin and terminus, and we placed this substituent on the bridgehead (1-) position when we found, after considerable preliminary work, that substituents on the benzo group did not impart sufficient differences to the two different positions in the olefin derived from the carbene to allow spectroscopic analysis. Finally, although the dioxygenated benzo group could have been avoided, the 5,8-dimethoxy substituents shifted the remaining aromatic protons far enough away from the olefinic protons in the ^1H NMR spectrum to facilitate spectroscopic analysis of the olefins **11b,c** derived from the carbenes **17** and **21**.

Reaction of carbomethoxycyclopentadiene (presumably a mixture of the 2 isomer and the 3 isomer) with *p*-benzoquinone gave a quantitative yield of a 3:1 mixture of Diels–Alder adducts **6** and **7**. Adduct **7** could be isolated in 30% yield by fractional crystallization from ether. Preferably, however, the mixture of **6** and **7** in dichloromethane was treated at room temperature with a small amount of concentrated hydrochloric acid and isomerized to a mixture of the corresponding hydroquinone derivatives, from which **8** could be isolated as a monohydrate (62%) by recrystallization from aqueous methanol. The quinol **8** was dimethylated to give **9** (87%) using potassium *tert*-butoxide and dimethyl sulfate in THF. Reduction of **9** with $LiAlH_4$ in ether gave alcohol **10** (92%), which was then protected using *tert*-butyldimethylsilyl chloride and imidazole in dry dimethylformamide[10] to give **11** in 86% yield. Treatment of **11** with disiamylborane in THF at −75 °C, followed by aqueous basic hydrogen peroxide, gave a mixture of regioisomers **12** and **13**, which could be separated by chromatography on alumina. The isolated yields of **12** and **13** using this procedure were 8 and 39%, whereas if borane in THF at 25 °C was used, the yields were 14 and 39%, respectively.

Scheme I



Consistent with the assigned structures, isomer **12** was much more mobile chromatographically, but much slower to oxidize under Oppenauer conditions than **13**. Thus oxidation of **13** using *p*-benzoquinone and tris(*tert*-butoxy)aluminum in refluxing benzene[11] required only 12 h for complete reaction (IR monitoring), whereas under the same conditions **12** required 72 h. Ketones **14a** and **18a** were isolated in 39 and 37% yields, respectively, after chromatography on alumina. The deuterated ketones **14b–d** and **18b–d** were then obtained by H–D exchange reactions using a slight modification of Tidwell's procedure.[12] Table I summarizes the deuterium content in these ketones.

The ^{1}H NMR spectra of **14a** and **18a** clearly establish their identities, particularly with respect to the location of the carbonyl group. Thus the methylene α to the carbonyl in **14a** gave an AB quartet centered at δ 2.09 ppm, J_{AB} = 17.0 Hz, ν_{AB} = 60.7 Hz, with the upfield doublet split further into doublets, J' = 4.0 Hz. This latter coupling is rationalized as W coupling[13] between the endo-2H and the proton syn to the aromatic ring on the bridging methylene group. This assigns the upfield (B) doublet of the AB quartet as due to the endo proton, and the deuterium exchange experiments confirm these assignments (vide infra). Ketone **14b** gave no resonance in the region assigned to the exo-H (A doublet of the AB quartet) and the upfield (B) doublet of doublets collapsed to a broadened doublet (H–D coupling) with a coupling constant of 4.0 Hz. The dideuterated material **14c**, of course, gave no absorption centered at δ 2.09, but **14d** showed the absence of resonance in the B portion of the AB quartet, and the A doublet collapsed to a broadened singlet. With **18a**, the methylene unit α to the carbonyl also gave an AB quartet centered at δ 2.19, J_{AB} = 17.0 Hz, ν_{AB} = 30.1 Hz, but in contrast to **14a**, *both* the A and B doublets were further split. The downfield (A) doublet was split cleanly into doublets, J' = 3.4 Hz, and the upfield doublets were split into multiplets which were not well resolved. These splittings may be rationalized on the basis that both exo- and endo-3H couple with the bridgehead (4) proton, but only the endo-3H undergoes W coupling[13] with the proton on the bridging methylene group. Here also, deuterium exchange experiments confirm these assignments. Thus, similar to **14b**, **18b** exhibited an ^{1}H NMR spectrum in which the downfield (A) resonance was not present, and the upfield doublet of multiplets collapsed to an ill-resolved narrow multiplet, while **18d** gave rise to the disappearance of the upfield (B) resonance and the collapse of the downfield (A) doublet of doublets to an ill-resolved doublet.

Table I. Percentage (±2) Deuterium Content of Ketones 14b–d and 18b–d[a]

	14b	14c	14d	18b	18c	18d
d_0	0	0	8	6	1	5
d_1	93	0	81	93	5	83
d_2	7	100	11	1	94	12

[a] Registry no.: **14b**, 61149-99-3; **14c**, 61195-73-1; **14d**, 61247-13-0; **18b**, 61740-98-5; **18c**, 61740-99-6; **18d**, 61769-49-1.

The Bamford–Stevens Thermolysis Route to Carbenes 17 and 21. The tosylhydrazones **15b,d** and **19b,d** were prepared in quantitative yields under neutral conditions from the corresponding ketones and *p*-tosylhydrazide in methanol solution at 60 °C for 1.3 h. The residue, obtained after concentration of the reaction mixture and evacuation at 70 °C (20 μ) for 2.5 h, was dissolved in THF and treated with *n*-butyllithium at −77 °C. The resulting solution was concentrated and evacuated at 70 °C (20 μ) for 1.5 h to give the lithium salts **16b,d** and **20b,d** as glasses. The salts were then decomposed in cyclohexane solution in a thick-walled glass tube by immersion in an oil both at 190 °C for 40 min. An unexceptional extractive workup followed by careful chromatography on alumina led to isolation of olefins **11a–d** in yields of 14–22%, as shown in Table II. Mass spectrometric analysis gave the distribution **11a:11b** + **11c:11d** (Table II), and indicated that little H–D exchange had occurred (compare deuterium content of ketones in Table I and olefins in Table II).

The exo/endo (x/n) migratory ratios required ^{1}H NMR analysis of the d_1 olefins (**11b,c**) in the olefinic region. The spectrum in this region consisted of a singlet at δ 6.49 ppm (aromatic protons) and an AB quartet centered at δ 6.74, with ν_{AB} = 11.1 Hz and J_{AB} = 5.2 Hz. The downfield (A) doublet was further split into doublets, J' = 3.0 Hz, and on this basis may be assigned to the proton at the 3 position, which is coupled to the bridgehead (4) proton.[14] With these assignments, analysis of the product olefins was possible. Thus, from the sequence **14b** → **15b** → **16b** → **11**, the H/D migratory ratio was determined to be ⅛ as follows. The ^{1}H NMR spectrum in the

Table II. Analysis of Olefins 11 Obtained from Thermolysis of 16b,d and 20b,d

Registry no.	Starting salt	% 11 isolated	% distribution[c] 11a	11b	11c	11d	Mig. ratio H/D	Mig. ratio H_x/H_n	$(E_a^n - E_a^x)^{190}$ °C, kcal/mol
61848-85-9	**16b**	21[a]	3	78	10	9	1/8		
								13	2.4
61490-24-2	**16d**	22[a]	11	3.5	79.5	6	23/1		
61788-00-9	**20b**	14[b]	3	12	81	4	1/7		
								18	2.7
61848-86-0	**20d**	20[b]	6	80.3	1.7	12	47/1		

[a] Average of two runs. [b] Single determination. [c] The ratios **11a:11b + 11c:11d** (±2%) were obtained mass spectrometrically. The ratios of **11b:11c** were obtained by ^{1}H NMR integration. Registry no.: **11a**, 61741-00-2; **11b**, 61195-72-0; **11c**, 61150-00-3; **11d**, 61827-39-2.

above-described olefinic region exhibited two absorptions, the major one at δ 6.68[5] (δ 6.74 − $\nu_{AB}/2$) as a singlet, and the minor absorption at δ 6.79[5] (δ 6.74 + $\nu_{AB}/2$) as a doublet (J' = 3.0 Hz, vide supra). These two absorptions are thus assigned to the D-migration (**11b**) and H-migration (**11c**) products, respectively. Multiple integrations (both electronic and planimetric) coupled with a small correction for the presence of 3% **11a** gave the ratio of **11b** to **11c** as 8:1 (Table II). Analogous procedures for the other three monodeuterated ketones generated the data in columns 3–7 in Table II.

The migratory ratios H_x/H_n can then be derived for the two regioisomeric carbenes **17a** and **21a** as follows. It is necessary to assume the same kinetic isotope effect (kie) for both exo and endo migration. Thus, for **17a**, the kie is obtained from the equations y/x = 7.8 and yx = 23, where x = the kie and y = the migratory ratio H_x/H_n. These calculations lead to a kie = 1.7 for **17** and 2.6 for **21**,[15] and to the migratory ratios shown in Table II. Assuming similar preexponential factors, these data lead to substantial activation energy differences for migration tendencies at 190 °C: $(E_a^n - E_a^x)^{190°C}$ ~2.4–2.7 kcal/mol.

Attempted Determination of Photolytic Migratory Aptitudes in 17 and 21. Numerous attempts at product analysis of the photolysis of **16** and **20** were unsuccessful. These salts were photolyzed using various combinations of suspensions in cyclohexane, solutions in dichloromethane or THF, with 254-nm light (Vycor), and a medium-pressure mercury lamp (Pyrex filter). Although one volatile product was formed during the photolysis as observed by GLC, this was not the olefin, as it had a longer retention time, and it disappeared during the course of the photolysis. Attempts to isolate and characterize this material failed. We did establish that olefin **11** was photolabile, but its rate of decomposition was such that it should have been observable if formed in the photolysis of **17** or **21** unless some species in the reaction mixture were sensitizing the photodecomposition of **11**.

Concluding Remarks. Similar to the bicyclo[2.2.1] carbocation situation, the origin of this propensity for H_x migration is at present not well understood.[17,18] It can be argued that the approximately tenfold greater tendency toward H_x migration in **2** than in **17** or **21** is due to a more favorable orbital alignment of H_x with the empty orbital on the carbene center in **2** than in **17** or **21**. We feel, however, that until it is understood why H_x migration is favored in the "unbiased" systems such as **17** and **21**, conclusions concerning orbital alignments drawn from migratory ratios derived from bi- and tricyclic systems are on tenuous grounds.

Experimental Section

Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Infrared spectra (IR) were recorded on a Perkin-Elmer 237B grating spectrophotometer.

Proton magnetic resonance spectra (^{1}H NMR) were obtained on Perkin-Elmer R-12, Varian A-60, or Varian HA-100 instruments. Chemical shifts are given as parts per million (ppm) downfield from tetramethylsilane in δ units and coupling constants are reported in hertz. Multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Mass spectra were determined on a CEC-21-100 high-resolution instrument or a Du Pont 21-491 instrument.

Gas chromatographic analyses were performed on either a Varian-Aerograph 2720 (thermal conductivity detector) or 2740 (flame ionization detector) instrument using either 5% or 20% SE-30 on Gas Chrom Q, packed in stainless steel columns (6 ft by 0.188 in. or 6 ft by 0.125 in.). Peak area measurements were obtained with the aid of a Vidar 6300 digital integrator.

1-Carbomethoxy-*endo*-tricyclo[6.2.1.^{2,7}]undeca-4,9-diene-3,6-dione (7). Carbomethoxycyclopentadiene dimer (36.0 g, 0.145 mol) was cleaved distillatively (dry ice trap) to give the monomer diene esters (18.0 g, 50%), bp 100–120 °C (25 mm). This was dissolved in dichloromethane (40 mL) at −75 °C and added in one portion to *p*-benzoquinone (16.7 g, 0.155 mol) suspended in benzene (80 mL) at 25 °C. The solution was stirred overnight, the solvent was evaporated, and excess benzoquinone was removed under high vacuum (40 °C, 10 μ, 2.5 h) to afford a 3:1 mixture of the isomeric adducts **6** and **7**, respectively (^{1}H NMR **6**, q_{AB} centered at δ 6.23 vs. **7**, br d, δ 6.97). Fractional crystallization from ether afforded isomerically pure **6** as pale yellow needles (10.1 g, 30%): mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 6.61 (s, 2 H), 6.20 (q_{AB}, ν_{AB} = 9.8 Hz, J_{AB} = 5.5 Hz, upfield (B) doublet further split, J' = 3.0 Hz, 2 H), 3.83 (s, 3 H), 3.60 (m, 3 H), 1.81 (m, 2 H): IR ($CHCl_3$) 1735, 1670, 1605 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.18; H, 5.33.

1-Carbomethoxy-5,8-dihydroxybenzonorbornadiene Monohydrate (8). Concentrated hydrochloric acid (0.3 mL) was added with vigorous stirring to the mixture of quinone adducts **6** and **7** (15.5 g, 66.8 mmol) in dichloromethane (25 mL). After 2 h, the solvent was evaporated to leave a tan solid (15.5 g, 100%). Recrystallization (MeOH–H_2O, 1:2 v/v) gave isomerically pure 8 H_2O as white crystals (10.3 g, 62%): mp 99–103 °C; ^{1}H NMR (acetone-d_6) δ 8.6–8.25 (br s, 1 H), 8.1–7.45 (br s, 1 H), 6.84 (m, 2 H), 6.36 (d, J = 1.5 Hz, 2 H), 4.18 (m, 1 H), 3.82 (s, 3 H), 3.46 (br s, 2 H), 2.41 (d, J = 1 Hz, 2 H); IR (KBr) 3315, 1715 m^{-1}.

Anal. Calcd for $C_{13}H_{12}O_4 \cdot H_2O$: C, 62.39; H, 5.64. Found: C, 62.56; H, 5.55.

1-Carbomethoxy-5,8-dimethoxybenzonorbornadiene (9). The quinol ester **8** (10.75 g, 139 mmol) and dimethyl sulfate (52.5 g, 417 mmol) in dry THF at 0 °C under nitrogen were treated with three portions of potassium *tert*-butoxide (3 × 5.19 g, 139 mmol) at 1-h intervals. The mixture was stirred overnight and filtered and the filtrate was dried ($MgSO_4$), and then concentrated to give a brown solid. Recrystallization (hexane) gave white needles (10.5 g, 87%), mp 77–80 °C. An analytical sample was prepared by thermal gradient sublimation (70 °C, 10 μ) to give white needles: mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 6.92 (q_{AB}, ν_{AB} = 14 Hz, J_{AB} = 5.5 Hz, upfield (B) doublet further split, J' = 3 Hz, 2 H), 6.51 (s, 2 H), 4.20 (m, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 2.51 (q_{AB}, ν_{AB} = 11 Hz, J_{AB} = 7 Hz, upfield (B) doublet further split, J' = 1.5 Hz, 2 H); IR ($CHCl_3$) 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.31; H, 6.12.

1-Hydroxymethyl-5,8-dimethoxybenzonorbornadiene (10). The ester **9** (9.00 g, 34.6 mmol) in dry ether (125 mL) was added dropwise to $LiAlH_4$ (1.14 g, 30.0 mmol) in ether (200 mL) at 0 °C and then stirred overnight at 25 °C. The cooled (0 °C) mixture was treated

successively with water (1.14 mL), 3 N aqueous sodium hydroxide (1.14 mL), and water (3.42 mL). After vigorous stirring (1 h) the mixture was filtered, the filter cake washed with ether, and the combined organic portions dried ($MgSO_4$) and concentrated to give a viscous, tan oil (8.10 g, 92%). The oil solidified upon standing and recrystallization (hexane) afforded white needles: mp 68–69.5 °C; ^1H NMR ($CDCl_3$) δ 6.82 (m, 2 H), 6.53 (s, 2 H), 4.13 (m, 4 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.17 (m, 2 H); IR ($CHCl_3$) 3485 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.39; H, 6.67.

1-(*tert*-Butyldimethylsiloxy)methyl-5,8-dimethoxybenzonorbornadiene (11a). To a solution of alcohol **10a** (6.70 g, 28.9 mmol) and imidazole (2.26 g, 33.2 mml) in dry dimethylformamide (100 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride[10] (5.00 g, 33.2 mmol) and the mixture stirred for 2 h. After the addition of water (150 mL) the cloudy mixture was extracted with pentane (4 × 100 mL). The combined pentane extracts were then dried ($MgSO_4$) and concentrated to give a white solid (8.60 g, 86%). An analytical sample was prepared by thermal gradient sublimation (70 °C, 10 μ) to give white needles: mp 92.5–93.5 °C; ^1H NMR ($CDCl_3$) δ 6.74 (q_{AB}, ν_{AB} = 11.1 Hz, J_{AB} = 5.2 Hz, downfield (A) doublet further split, J' = 3.0 Hz, 2 H), 6.49 (s, 2 H), 4.49 (q_{AB}, ν_{AB} = 31 Hz, J_{AB} = 11 Hz, 2 H), 4.12 (m, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 2.27 (q_{AB}, ν_{AB} = 30 Hz, J_{AB} = 7 Hz, both doublets (A and B) further split, J' = 2 Hz, 2 H), 0.91 (s, 9 H), 0.125 (s, 3 H), 0.115 (s, 3 H); MS (70 eV) *m/e* (rel intensity) 346 (7), 289 (100), 274 (90), 259 (31).

Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 69.32; H, 8.73. Found: C, 69.35; H, 8.70.

1-(*tert*-Butyldimethylsiloxy)methyl-5,8-dimethoxybenzonorbornene-*exo*-3-ol (13) and 1-(*tert*-Butyldimethylsiloxy)-methyl-5,8-dimethoxybenzonorbornen-*exo*-2-ol (12). A. Hydroboration of 11 with Disiamylborane. A 1.3 M solution of BH_3·THF (102 mL, 133 mmol) was added to 2-methyl-2-butene (21.0 g, 300 mmol) in dry THF (150 mL) at 0 °C. The mixture was stirred at 25 °C for 2.5 h, then cooled to −75 °C. To this solution was added **11** (13.2 g, 38.2 mmol) in THF (75 mL). The reaction mixture was warmed slowly and stirred overnight and then excess borane was decomposed by the addition of ice chips after cooling (0 °C). When the foaming had subsided 3 N aqueous sodium hydroxide (70 mL) was added followed by 30% aqueous hydrogen peroxide (70 mL) and the mixture was stirred for 2 h. The organic layer was separated, the THF was removed, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic portions were washed with 1 M hydrochloric acid, 5% aqueous sodium bicarbonate, and brine and dried ($MgSO_4$). The solvent was evaporated to give an oil (14.4 g) which contained a mixture of the isomers **12** and **13**.

Chromatography (alumina, CH_2Cl_2) afforded separation of the two isomers. The faster moving component, **12**, was obtained as a mobile, colorless oil (1.10 g, 8%). An analytical sample was prepared by distillation (Kugelrohr, 105 °C, 20 μ): ^1H NMR ($CDCl_3$) δ 6.59 (s, 2 H), 4.65 (q_{AB}, ν_{AB} = 42.5 Hz, J_{AB} = 11 Hz, 2 H), 4.52 (br s, 1 H), 4.00 (m, 1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.50 (m, 1 H), 2.01 (br q_{AB}, ν_{AB} = 42 Hz, J_{AB} = 9 Hz, 2 H), 1.78 (m, 2 H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.12 (s, 3 H); IR ($CHCl_3$) 3500 cm^{-1}.

Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 65.94; H, 8.67.

The slower moving isomer, **13**, was a viscous, colorless oil (5.42 g, 39%). An analytical sample was prepared by distillation (Kugelrohr, 105 °C, 20 μ): ^1H NMR ($CDCl_3$) δ 6.60 (s, 2 H), 4.30 (br s, 2 H), 4.01 (m, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.42 (m, 1 H), 1.97 (complex m, 5 H), 0.92 (s, 9 H), 0.09 (s, 6 H); IR ($CHCl_3$) 3580, 3400 cm^{-1}.

Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 65.66; H, 8.83.

The intermediate chromatography fractions contained a mixture of the two isomers (1.35 g).

B. Hydroboration of 11 with Borane. A 1.3 M solution of BH_3·THF (10 mL, 13 mmol) was added to the olefin **11** (2.97 g, 8.58 mmol) in dry THF (50 mL) at 0 °C. The solution was allowed to warm to room temperature and then to stir for 4 h. Workup as above gave an oil (2.86 g) consisting of a mixture of **12** and **13**, which were isolated in yields of 14 and 39%, respectively, by chromatography as described above.

1-(*tert*-Butyldimethylsiloxy)methyl-5,8-dimethoxybenzonorbornen-3-one (14a). A mixture of alcohol **13** (5.02 g, 13.74 mmol), *p*-benzoquinone (2.00 g, 18.5 mmol), and tris(*tert*-butoxy)aluminum (7.35 g, 29.9 mmol) in benzene (200 mL) was heated at reflux for 12 h. The cooled mixture was stirred with 10% aqueous sulfuric acid (510 mL) for 1 h. The organic layer was separated, washed with 10% aqueous sulfuric acid (2 × 100 mL), 10% aqueous sodium hydroxide (until the aqueous washes remained colorless), water, and brine, dried ($MgSO_4$), and concentrated to give a yellow solid (3.88 g). Chromatography (alumina, pentane/CH_2Cl_2, 7:3 v/v) gave a white solid (1.92 g, 39%), mp 117–119 °C. An analytical sample was obtained from thermal gradient sublimation (105 °C, 10 μ) as fine, white crystals: mp 118–119 °C; ^1H NMR ($CDCl_3$) δ 6.68 (s, 2 H), 4.36 (q_{AB}, ν_{AB} = 28.0 Hz, J_{AB} = 11.0 Hz, 2 H), 3.85 (m, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.09 (q_{AB}, ν_{AB} = 60.7 Hz, J_{AB} = 17.0 Hz, upfield (B) doublet split further into doublets, J' = 4.0 Hz, 2 H), 2.30 (m, 2 H), 0.91 (s, 9 H), 0.10 (s, 6 H); IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 362 (4), 305 (100), 262 (15), 248 (22), 189 (28).

Anal. Calcd for $C_{20}H_{30}O_4Si$: C, 66.26; H, 8.34. Found: C, 66.19; H, 8.32.

1-(*tert*-Butyldimethylsiloxy)methyl-5,8-dimethoxybenzonorbornen-2-one (18a). A mixture of alcohol **12** (1.02 g, 280 mmol), *p*-benzoquinone (0.417 g, 3.86 mmol), and tris(*tert*-butoxy)aluminum (1.55 g, 6.30 mmol) in benzene (40 mL) was heated at reflux for 72 h. Workup as above and chromatography (alumina, pentane/CH_2Cl_2, 2:1 v/v) gave **18a** as a white solid (375 mg, 37%). An analytical sample was prepared by thermal gradient sublimation (105 °C, 20 μ) to give white crystals: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 6.62 (q_{AB}, ν_{AB} = 8 Hz, J_{AB} = 9 Hz, 2 H), 4.41 (q_{AB}, ν_{AB} = 43 Hz, J_{AB} = 11 Hz, 2 H), 3.78 (s) + 3.76 (m) + 3.69 (s) (total 7 H), 2.37 (m, 2 H), 2.19 (q_{AB}, ν_{AB} = 30.1 Hz, J_{AB} = 17.0 Hz, downfield (A) doublet split further into doublets, J' = 3.4 Hz, upfield (B) doublet split into poorly resolved multiplets, 2 H), 0.88 (s, 9 H), 0.09 (s, 6 H); IR ($CHCl_3$) 1745 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 332 (3), 305 (100), 262 (12), 248 (13), 189 (15).

Anal. Calcd for $C_{20}H_{30}O_4Si$: C, 66.26; H, 8.34. Found: C, 66.50; H, 8.54.

Preparations of the Deuterio Derivatives of 14. A. 1-(*tert*-Butyldimethylsiloxy)methyl-2-*exo*-deuterio-5,8-dimethoxybenzonorbornen-3-one (14b). To ketone **14a** (937 mg, 2.59 mmol) in dry dioxane (50 mL) was added potassium *tert*-butoxide (415 mg, 3.17 mmol) dissolved in deuterium oxide (25 mL). The mixture was heated at 60 °C for 1.25 h and quenched with a mixture of saturated aqueous ammonium chloride (50 mL) and dichloromethane (70 mL). The layers were separated and the aqueous portion extracted with pentane (5 × 40 mL). The combined organic portions were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford **14b** (909 mg, 95%) as a white solid.

Mass spectral analysis of the base peak region (*m/e* 305–309) gave the ratios of d_0:d_1:d_2 = 0:93:7 (±2). The ^1H NMR analyses of **14b**, **14c**, and **14d** are described in the body of the paper.

B. 1-(*tert*-Butyldimethylsiloxy)methyl-2,2-dideuterio-5,8-dimethoxybenzonorbornen-3-one (14c). To ketone **14a** (2.32 g, 6.41 mmol) in dioxane (120 mL) was added potassium *tert*-butoxide (0.90 g, 8.0 mmol) dissolved in deuterium oxide (60 mL). The mixture was stirred at 60 °C for 96 h and worked up as above. Some of the silyl protecting group had been removed during the long reaction period, so the mixture was resilylated in the usual way to give **14c** (2.20 g, 95%).

Mass spectral analysis gave d_0:d_1:d_2 = 0:0:100 (±2).

C. 1-(*tert*-Butyldimethylsiloxy)methyl-2-*endo*-deuterio-5,8-dimethoxybenzonorbornen-3-one (14d). Treatment of **14c** (2.20 g, 6.04 mmol) in dioxane (120 mL) with potassium *tert*-butoxide (0.90 g, 8.0 mmol) dissolved in water (60 mL) at 60 °C for 2.6 h followed by workup and reprotection of the desilyated material (~10%) gave **14d** (2.14 g, 97%).

Mass spectral analysis gave d_0:d_1:d_2 = 8:81:11 (±2).

Preparations of the Deuterio Derivatives of 18. Compounds **18b, 18c,** and **18d** were prepared by procedures parallel to those for compounds **14b–d**. The deuterium contents of the materials are given in Table I.

Preparation of the Tosylhydrazone Derivatives and Their Lithium Salts. The following is a representative procedure. The ketone **14b** (1.84 g, 5.07 mmol) was dissolved in absolute methanol (180 mL) at 60 °C, *p*-toluenesulfonylhydrazide (0.99 g, 5.32 mmol) was added, and the mixture was stirred at 60 °C for 1.3 h. The solution was concentrated and the residue warmed under vacuum (70 °C, 20 μ, 2.5 h). The resulting solid was dissolved in dry THF (50 mL) and treated at −75 °C under nitrogen with a 1.34 M hexane solution of *n*-butyllithium (4.73 mL, 6.34 mmol). The resulting solution was warmed slowly to 25 °C and concentrated, and the residue was heated under vacuum (70 °C, 20 μ, 1.5 h) to give a glass **16b** (2.46 g).

Pyrolysis of the Tosylhydrazone Salts 16 and 20. A representative procedure is as follows. The salt **16b** (827 mg, 1.77 mmol) was suspended in dry cyclohexane (~20 mL) in a Fisher-Porter combustion tube vessel with an aluminum and Teflon sealing disk and standard pipe coupling. The tube was heated in an oil bath (190 ± 2 °C) for 40 min. After cooling, the reaction mixture was partitioned be-

tween water (20 mL) and dichloromethane (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow solid (460 mg). Chromatography (alumina, pentane/CH_2Cl_2, 9:1 v/v) gave the olefin **11** (22%) (see Table II).

Mass spectral analysis (*m/e* 289–294 cluster) determined the ratio **11a:11b** + **11c:11d** (Table II). The ^1H NMR analyses of the olefinic mixtures were carried out as described in the body of the paper.

Photolyses of 1-(*tert*-Butyldimethylsiloxy)methyl-5,8-dimethoxybenzonorbornadiene (11). A. The olefin **11** (12.9 mg, 0.037 mmol) in degassed dichloromethane (1 mL) with octadecane (5.5 mg, 0.022 mmol) as an internal standard was photolyzed in a Pyrex tube with a Hanovia 450-W medium-pressure mercury arc lamp contained in an ice–water-cooled Pyrex well. The course of the reaction was monitored by flame ionization GLC (6 ft × 0.125 in., SE-30 5% on Gas Chrom Q). The concentration of **11** decreased (only 52% remaining after 2 h 40 min and <23% after 5 h) and a new peak arose having a longer retention time than that of the olefin (**11**). After 3.5 h the new peak began to decrease and was absent after 5.5 h.

B. The olefin **11** (12.5 mg, 0.036 mmol) in degassed cyclohexane (1 mL) in a Vycor tube was irradiated in a Rayonet photochemical reactor (254 nm) and the reaction was followed by GLC as above. Similar results to the first photolysis were noted as the olefin concentration decreased, although more rapidly (<50% olefin remained after 1.5 h), and the new peak of longer retention time arose and then rapidly decreased. After 2.5 h both the olefin peak and the unknown peak were absent from the GLC trace.

Attempts to Isolate the Unknown Compound Formed in the Photolysis of 11. A solution of **11** (80 mg, 0.23 mmol) in degassed dichloromethane (5 mL) was irradiated (254 nm) for 2.4 h in a Pyrex tube. After removal of the solvent the residue was chromatographed ("dry column", Al_2O_3/CH_2Cl_2). Three bands showing ultraviolet activity were removed but none contained the unknown material (by GLC). The remaining Al_2O_3 sections were washed with dichloromethane. The combined washes were concentrated to give an oil (~4 mg) which gave a major GLC peak at the same retention time as the unknown compound. This material was analyzed by GC/MS: major peaks at *m/e* 346, 289, 274, 259, 215, and 57. This spectrum was very similar to that of **11**, except that *m/e* 57 was reduced in intensity, and *m/e* 215 was much increased relative to those in the spectrum of **11**. No further attempts were made to isolate and identify this unknown material.

Photolysis of the Tosylhydrazone Salt 16a. A. A suspension of **16a** (121 mg, 0.26 mmol) in degassed cyclohexane (2 mL) was irradiated (254 nm) in a Vycor tube. No olefin **11** formation was detectable (GLC and TLC) and a new, longer retention peak (the same unknown GLC peak seen in photolysis of **11** above) arose slightly but disappeared upon further irradiation (~3 h).

B. A degassed cyclohexane (2 mL) suspension of **16a** (100 mg, 0.21 mmol) in a Pyrex tube was irradiated with a Hanovia 450-W medium-pressure Hg arc lamp. Results essentially identical with the above photolysis were obtained. No olefin **11** formation was detectable (GLC and TLC).

C. Further experiments using homogeneous solutions (CH_2Cl_2 and THF) of **16a** resulted in similar negative results.

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Registry No.—**6**, 61741-01-3; **7**, 61769-50-4; **8**, 61741-02-4; **9**, 61149-94-8; **10a**, 61741-03-5; **12**, 61149-97-1; **13**, 61149-96-0; **14a**, 61149-98-2; **18a**, 61741-04-6; monomer diene ester, 61741-07-9; *p*-benzoquinone, 106-51-4; *tert*-butyldimethylsilyl chloride, 18162-48-6.

References and Notes

(1) (a) This work was presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 29–Sept 30, 1976, No. ORGN-095. (b) A preliminary report has appeared: E. P. Kyba and C. W. Hudson, *J. Am. Chem. Soc.*, **98**, 5696 (1976).
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(15) The latter number is considerably less reliable, since it was obtained from single determinations due to unavailability of sufficient amounts of **18b** and **18d**. If the difference is real we have no rationalization for it. The kie's >1 are in accord with Nickon's observations for **2**,[4] but differ from the results of Kirmse,[16] who found kie = 1.00 for the *thermal* generation of 2-H and 2-D-1-propylidene.
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Reaction of 2-Norbornyl- and 3,3-Dimethyl-2-norbornylmagnesium Bromide with Acetone

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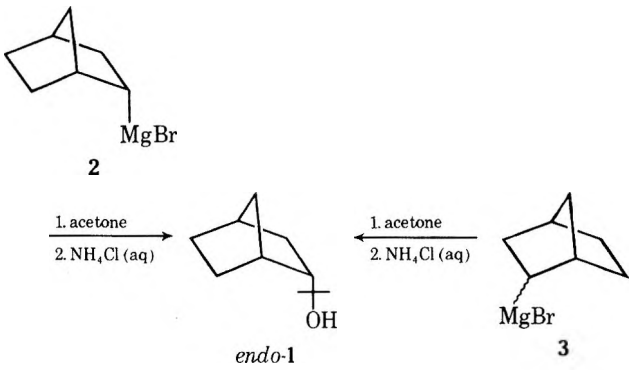
Attempts to determine the stereochemistry of electrophilic addition of acetone to two configurationally rigid Grignard reagents [2-norbornylmagnesium bromide (3) and 3,3-dimethyl-2-norbornylmagnesium bromide (9)] are described. Evidence is presented which suggests that the reaction of 9 with benzophenone proceeds via an electron-transfer pathway. In addition, results describing an improved synthesis of camphenilone and the stereospecific synthesis of *exo*-2-bromo-3,3-dimethylnorbornane are presented.

Despite its long-standing synthetic importance, a detailed understanding of the reaction of Grignard reagents with carbonyl compounds has only recently begun to emerge.[2,3] The products of such reactions indicate that several, frequently competitive reaction pathways are available: (a) direct 1,2-addition, (b) electron transfer, (c) reduction (when a β hydrogen is present in the Grignard reagent), and (d) enolization (if the ketone contains α protons).

The role of electron-transfer processes in the reaction of Grignard reagents with certain ketone substrates is well documented.[2,3] In general, however, it is believed that such processes play a relatively minor role in the overall addition of organomagnesium reagents to ketones, becoming important only when the structure of the ketone is such that its one-electron reduction results in a relatively stable ketyl. To be sure, the stability of the intermediate ketyl is an important point in considering the extent to which an electron-transfer component participates in the reaction of a ketone with a Grignard reagent. Such participation, however, cannot be ascertained with certitude by existing direct (ESR) or indirect (kinetic and product studies) evidence. In an effort to determine the extent, if any, that single-electron transfer processes are involved in such reactions, we have examined the reaction of two stereochemically rigid organomagnesium reagents with acetone, reasoning that a concerted reaction might be expected to lead to products with retained or inverted stereochemistry while a nonconcerted process such as electron transfer might be expected to yield, in general, products with loss of stereochemistry. Specifically, we chose to examine the reaction of acetone with *endo*- and *exo*-2-norbornyl- and *endo*- and *exo*-3,3-dimethyl-2-norbornylmagnesium bromide. Although our ultimate objective proved elusive, we describe here the procedures and results in the hope that others will benefit from these findings.

Results and Discussion

An equilibrium mixture of 2-norbornylmagnesium bromide (60% endo, 40% exo) was converted to *endo*-2-norbornylmagnesium bromide (>97% endo) by treatment with benzophenone according to published procedures.[4] The resulting mixture was allowed to react at 0 °C with an excess of dry acetone. Following an unexceptional workup, the sole addition product was isolated and its structure assigned as *endo*-**1**. This assignment is based on an interpretation of the ^{1}H NMR data in Table I and its comparison with prior studies of the ^{1}H NMR spectra of norbornanes.[5] Briefly, endo substitution in 2-substituted norbornanes is easily distinguishable from exo configuration on the basis of the magnitude of the vicinal coupling constant, with representative ranges for coupling constants in these configurations being $J_{2x,3x}$ = 4–12, $J_{2n,3n}$ = 4–7, and $J_{3x,3n}$ = 2–4 Hz. In addition, coupling between a bridgehead proton and its vicinal exo proton is significant ($J_{1,2x}$ = 2.5–4.5 Hz) while the corresponding coupling to the vicinal endo proton is small. Moreover, coupling between the endo proton at the 2 or 3 position and the anti-7 proton is significant ($J_{2n,7'}$ = 2–4 Hz) while the coupling to the corresponding exo proton ($J_{2x,7'}$) is small. Repetition of this experiment employing an equilibrium mixture of 2-norbornylmagnesium bromide produced the same epimeric distribution of 1 (i.e., >97% endo) in 48% yield.

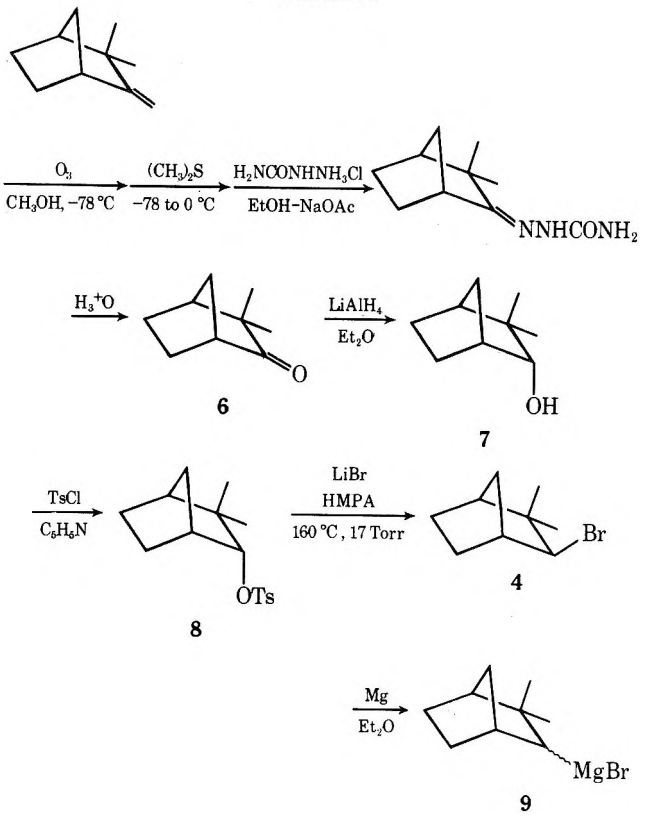


The failure to observe *exo*-**1** in the product mixture resulting from the reaction of 2-norbornylmagnesium bromide with acetone is not a consequence of its instability under reaction or isolation conditions. This point was demonstrated by the fact that authentic *exo*-**1**, admixed with acetone and treated with 2-norbornylmagnesium bromide, could be isolated together with *endo*-**1** by preparative GLC. The composition of this epimeric mixture was readily established by ^{1}H NMR analysis in the presence of the shift-inducing reagent Eu(fod)$_3$ as well as GLC analysis.

Because stereochemical conclusions based on a comparison of the starting and product geometries of differing geometrical (in contrast to optical) isomers are valid only in the demonstrated absence of processes leading to epimerically selective reactions (e.g., the kinetically favored or disfavored reaction of one epimer), the absence of any detectable quantity of *exo*-**1** from the reaction of **3** with acetone precludes a conclusive statement regarding the stereochemistry of the carbon–carbon bond forming step in the reaction of 2-norbornylmagnesium bromide with acetone. Reasoning that the absence of *exo*-**1** in the addition of **3** to acetone might, in view of the geometric considerations of the norbornyl system, result from a preference of *exo*-2-norbornylmagnesium bromide to participate in a reduction[6] rather than an addition process, we prepared and examined the reactions of 3,3-dimethyl-2-norbornylmagnesium bromide with acetone. The synthesis of the requisite bromide, 2-bromo-3,3-dimethylnorbornane (**4**), is outlined in Scheme I and merits brief discussion.

The preparation of camphenilone (**6**) has been reported by other workers.[7] The procedure described here provides a product of substantially improved purity with a considerable reduction in effort. The reduction of camphenilone with

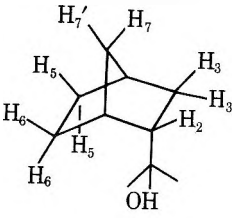
Scheme I



$LiAlH_4$ is sterospecific,[8] insofar as can be determined by ^1H NMR analysis, producing only *endo*-3,3-dimethylnorbornan-2-ol (*endo*-camphenilol, **7**). The conversion of **7** to its tosylate **8** was achieved by conventional procedures and requires no additional comment. The stereospecific conversion of **8** into *exo*-2-bromo-3,3-dimethylnorbornane (*exo*-**4**) was accomplished by reaction of **8** with anhydrous lithium bromide in HMPA at 160 °C under a reduced pressure. The stereospecific conversion of alkyl tosylates into the corresponding halide by treatment with LiX–HMPA is a established procedure.[9] However, the ability of LiX–HMPA to effect a stereospecific displacement at the 2 carbon on a 3,3-disubstituted norbornyl ring is noteworthy and suggests the remarkable and unique nucleophilic properties associated with this reagent mixture.

Varied attempts to prepare 3,3-dimethyl-2-norbornylmagnesium bromide (**9**) by classical procedures, i.e., by the direct reaction of **4** with magnesium turnings, produced, in substantial yield, a substance tentatively identified as bis(3,3-dimethyl-2-norbornane), presumably as a result of a Wurtz-like coupling process. These failures notwithstanding, solutions of 3,3-dimethyl-2-norbornylmagnesium bromide in ether were finally achieved by treating **4** with finely divided magnesium produced by the reaction of anhydrous magnesium bromide with sodium–potassium (78% K) alloy in refluxing ether. The epimeric distribution of an equilibrium mixture of **9** was established by a procedure developed to assay the isomer composition of 2-norbornylmagnesium bromide.[10] Thus, **9** is converted to 3,3-dimethyl-2-norbornyl(tri-*n*-butylphosphine)copper(I) (**10**), which on treatment with 3–5 equiv of methyllithium is converted to the corresponding methylate complex, **10a**. Oxidative coupling of **10a** with nitrobenzene at −78 °C yields 2,2,3-trimethylnorbornane (16% exo, 84% endo). A selective, albeit incomplete, epimer destruction of **9** can be achieved by treating it with a limiting quantity of benzophenone. Table II summarizes the epimer ratio produced by treating ether solutions of **9** with differing amounts of benzophenone at −78 °C.

Table I. Coupling Constants for Dimethyl(*endo*-2-norbornyl)carbinol[a]



endo-**1**

$J_{1,2x}$[b]	$J_{2x,3x} = 12.5$
$J_{3x,3n} = 12.5$	$J_{3x,5x} = 2.5$
$J_{2x,3n} = 6.2$	$J_{3x,4} = 4.5$
$J_{3n,7'} = 2.3$	

[a] Spectra were recorded at 100 MHz in CCl_4 containing ~1:1 (molar) $Eu(fod)_3$:*endo*-**1**. Coupling constants (J) are in hertz. Coupling constant assignments were confirmed by decoupling. Notation: x = exo, n = endo. A complete assignment of the coupling constants for all ring protons was precluded by the overlap between several resonances. [b] Strong coupling was observed between H_1 and H_{2x} but its magnitude could not be accurately determined because of overlapping interference from H_7.

Table II. The Distribution of *exo*- and *endo*-9 Produced by the Addition of Benzophenone to an Equilibrium Mixture of 9 in Ether at −78 °C

mmol **9**	mmol benzophenone	Mol %[a] *exo*-**9**:*endo*-**9**	
0.92	0.00	16	84
1.4	0.59	37	63
1.8	1.1	49	51
2.2	1.7	56	44

[a] Determined by analysis of the ratio of *exo*- to *endo*-2,2,3-trimethylnorbornane. See text for a discussion of assay procedure.

Three conclusions are immediately obvious from the data in Table II. First, the epimer distribution in an equilibrium mixture of 3,3-dimethyl-2-norbornylmagnesium bromide contains a noticeably higher fraction of endo epimer than does an equilibrium mixture of 2-norbornylmagnesium bromide, indicating that the endo isomer is slightly more stable in **9** than in **2**. Second, in contrast to 2-norbornylmagnesium bromide,[4] it is the endo isomer of 3,3-dimethyl-2-norbornylmagnesium bromide which is preferentially destroyed in the reaction of **9** with benzophenone. Third, these results establish that the reduction of a Grignard reagent can proceed by a pathway other than β-hydrogen elimination[6] and strongly suggest that *electron transfer may also play a role.*

The magnitude of the difference between the epimer ratio of an equilibrium mixture and that of a selectively enhanced mixture of **9** (entry 4, Table II), although less than that possible for 2-norbornylmagnesium bromide, is nonetheless sufficient to permit a conclusive statement regarding the stereochemistry of the carbon–carbon bond forming step in its reaction with acetone. To our dismay, however, the reaction of **9** with acetone produced none of the expected addition product. While a detailed examination of this result has not been carried out, labeling experiments are consistent with the conclusion that enolization has become the dominant reaction pathway. Thus, addition of acetone to an ether solution of **9** produced a reaction mixture which, when hydrolyzed with deuterium oxide, yielded 2,2-dimethylnorbornane (<2% d_1). By comparison, the 2,2-dimethylnorbornane isolated from the

direct protonolysis of **9** with deuterium oxide exhibited >98% d_1 incorporation.[11]

In summary, an attempt to determine the extent to which electron transfer is involved in the reaction of Grignard reagents with simple ketones,[12] by determining the stereochemistry of the addition product resulting from the reaction of two different configurationally rigid organomagnesium reagents with acetone, has proven inconclusive because of the dominating influence of certain side reactions. In related studies, an improved procedure for the preparation of camphenilone, a stereospecific synthesis of *exo*-2-bromo-3,3-dimethylnorbornane (a useful precursor to other camphenil and apoisobornyl compounds),[8] and the preparation of a stereochemically rigid organomagnesium reagent devoid of β hydrogens have been described.

Experimental Section

Organometallic reagents were manipulated using standard procedures. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 instrument equipped with a flame-ionization detector, employing unexceptional internal standard techniques. Preparative GLC was carried out using a Hewlett-Packard Model 710 equipped with a thermal conductivity detector. Except where otherwise indicated, the desired separations were achieved using an 8-ft, 20% UC-W98 silicone rubber on Chromosorb P column. Pyridine was dried by distillation from calcium hydride under nitrogen. Diethyl ether and THF were distilled from $LiAlH_4$ under nitrogen. Methyllithium was purchased from Foote Mineral Co., and analyzed by the Gilman double titration method. Ozone was generated using a commercially available ozone generator (PSI Ozonizer Model LOA-2). Commercially available camphene (Technical grade, 80–85%), dimethyl sulfide, semicarbazide hydrochloride, and sodium acetate were used without further purification. Sodium–potassium alloy (78% K) was purchased from MSA Research Corp.

All melting points and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. NMR spectra were determined with a Varian HA-100 NMR spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU 6 mass spectrometer. Analytical analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of Anhydrous $MgCl_2$. Into a 1-L, three-neck flask equipped with a Teflon-coated magnetic stirrer bar, reflux condenser, and 250-mL addition funnel was placed 24.3 g (1.00 g-atom) of magnesium turnings. The entire system was flame dried under a flush of nitrogen and allowed to cool before adding 500 mL of THF. The addition funnel was charged with 120 mL (150 g, 1.52 mol) of 1,2-dichloroethane which was added slowly to the reaction vessel until reflux commenced, at which point the rate of addition was adjusted to maintain a gentle reflux. As the reaction continued a white precipitate of magnesium chloride formed. Following the completion of addition the reaction mixture was stirred for an additional 60 min and finally heated at reflux overnight. The resulting mixture was filtered under nitrogen and the magnesium chloride collected in a fritted glass funnel and subsequently dried at 150 °C (0.2 Torr) for 3 days. The yield of $MgCl_2$ was 95 g (100%).

Camphenilone (3,3-Dimethylbicyclo[2.2.1]heptan-2-one, 6). A solution of 200 g (1.18 mol) of technical grade camphene in 1500 mL of methanol was placed in a 3-L, one-neck flask. The flask was chilled in a dry ice–acetone bath and a gas dispersion tube (Kontes 956500), attached to a gas inlet adapter (Kontes 181000), was inserted. The solution was treated with ozone (inlet flow rate 7–8 L/min) for 8 h with care taken to maintain a bath temperature <−70 °C. The gas dispersion tube was removed and 150 mL of dimethyl sulfide added. The flask was removed from the bath and a Teflon-coated magnetic stirring bar carefully added. The resulting solution was allowed to warm gradually with stirring. At ~0 °C an exothermic reaction developed and the pot temperature rose rapidly to ~45 °C. After 4 h, the clear to light yellow solution was transferred to a 3-L, three-neck flask and the contents subjected to steam distillation. A total of 3.5 L of distillant was collected. The crude distillant was extracted with three 500-mL portions of petroleum ether (bp 30–60 °C) and the combined extracts dried over magnesium sulfate. The resulting solution was concentrated on a steam bath to yield 210–225 g of a pale yellow liquid. This material was transferred to a 1-L flask containing 350 mL of an ethanol–water mixture (60:1). The flask was equipped with a reflux condenser and a Teflon-coated magnetic stirrer bar. Semicarbazide hydrochloride (69.8 g, 0.630 mol) and sodium acetate (111 g, 1.36 mol) were added and the resulting mixture refluxed with stirring for 12 h, then cooled to 0 °C and the crystalline white solid collected by suction filtration, washed with 500 mL of water followed by 500 mL of petroleum ether, and air dried. The yield of camphenilone semicarbazone (mp 222–223 °C, lit.[12] 222–224 °C) was 34–37%, based on camphene, and it is sufficiently pure to be used directly in the following reaction. If necessary, it can be recrystallized from hot ethanol–water (2:1). Camphenilone semicarbazone (190 g, 0.970 mol) was placed in a 2-L flask. Water (650 mL), ethanol (650 mL, 95%), and hydrochloric acid (325 mL, 12 M) were added and the resulting mixture refluxed for 2 h and allowed to cool before adding 1000 mL of water. The oil that separated was extracted with four 500-mL portions of petroleum ether. The combined extracts were dried over magnesium sulfate and concentrated on a steam bath. The residual oil was transferred to a 250-mL flask which was fitted with a short-path, wide-bore distillation head. Vacuum distillation afforded 99 g (68–74% based on semicarbazone) of camphenilone [bp 40–50 °C (0.2 Torr); mp (sealed capillary) 38.0–39.5 °C, lit.[13] 38.4 °C].

***endo*-Camphenilol (*endo*-3,3-Dimethylnorbornan-2-ol, 7)** (mp 70–73 °C, lit.[8] 71–74.5 °C) was prepared by the reduction of camphenilone as described by Brown and co-workers.[8]

***endo*-Camphenilol Tosylate (8).** *p*-Toluenesulfonyl chloride (210 g, 1.10 mol) was placed in a three-neck, 1-L flask equipped with a Teflon-coated magnetic stirrer bar, a drying tube, and a 250-mL addition funnel containing 7.60 g (0.543 mol) of *endo*-camphenilol in 100 mL of pyridine. Pyridine (450 mL) was added to the reaction flask. The solution of camphenilol was added rapidly with stirring at room temperature. This mixture was stirred at ambient temperature for 3 days during which time a white precipitate of pyridine hydrochloride formed. The resulting mixture was poured into 1500 mL of ice–water which was then extracted with five 300-mL portions of methylene chloride. The combined organic layers were extracted with five 500-mL portions of cold 1.8 M H_2SO_4, followed by two 500-mL portions of a saturated aqueous solution of sodium bicarbonate, and dried ($MgSO_4$). Concentration of this solution under reduced pressure yielded 155 g of crude product. Recrystallization was achieved by dissolution in a minimal amount of petroleum ether at room temperature, treatment of this solution with decolorizing charcoal, gravity filtration, and finally slow cooling in a dry ice–acetone bath. The white, crystalline product was collected by suction filtration and vacuum dried to yield 115 g (72%) of **8**: mp 59.5–60.5 °C; ^1H NMR δ ($CDCl_3$) 7.50 (AB pattern, 4 H, aryl) 4.18 (d, 1 H, HCOTs), 2.43 (s, 3 H, CH_3), and 0.70–2.40 (complex, 16 H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.37; H, 7.58.

***exo*-Camphenilyl Bromide (*exo*-2-Bromo-3,3-dimethylnorbornane, 4).** *Caution:* Hexamethylphosphorus triamide (HMPA) is a suspected carcinogen. This procedure should be carried out in a well-ventilated fume hood and appropriate precautions taken.

Into a 500-mL, one-necked flask equipped with a Teflon-coated stirrer bar and a short-path distillation head with 100-mL receiver was placed *endo*-camphenilyl tosylate (55.3 g, 0.187 mol), anhydrous lithium bromide (Research Organic/Inorganic, 26.3 g, 0.302 mol), and 200 mL of HMPA, distilled from calcium hydride under reduced pressure. Stirring was commenced as soon as possible and the pressure of the system was reduced to 16 Torr. The reaction flask was immersed in a oil bath heated to 160 °C and complete dissolution of all solids was soon noted. The volatiles that were produced as the reaction proceeded were collected in a chilled (−78 °C) receiver. Distillation was discontinued when the rate of distillant production slowed noticeably. The crude distillant (~80 mL) was added to 250 mL of petroleum ether and the resulting mixture extracted with four 250-mL portions of water, dried ($MgSO_4$), and concentrated on a steam bath. Fractionation of the residual liquid produced a forerun [6.62 g, bp 50–95 °C (17 Torr)] and a product-containing fraction [18.8 g, 50% yield, bp 100–101 °C (17 Torr)]. Fractionation of this material, which tends to solidify in the condenser, is aided by the use of a heat gun. *exo*-2-Bromo-3,3-dimethylnorbornane is a slushy semisolid at room temperature: ^1H NMR δ ($CDCl_3$) 3.60 (d, J = 2.0 Hz, 1 H, HCBr), 2.60–0.70 (complex, 15 H); *m/e* (rel intensity) 204 (7), 202 (7), and 67 (100).

2-Norbornylmagnesium bromide was prepared from *exo*-2-bromonorbornane using unexceptional procedures. Its stereochemistry was assayed by conversion to 2-methylnorbornane.[9]

***endo*-2-Norbornylmagnesium bromide** was prepared by the method of Jensen and Nakamaye.[4] Reference 9 describes the details of this procedure.

3,3-Dimethyl-2-norbornylmagnesium Bromide (9). Attempts to prepare **9** in ether by traditional methods yielded solutions with unusually low titer values. Examination of a hydrolyzed aliquot indicated that a substantial fraction of the starting bromide had been

converted to a hydrocarbon product, the mass spectrum of which was consistent with its assignment as bis-2-(3,3-dimethylnorbornane). Repetition of this procedure using 12.3 g (61.0 mmol) of **4**, 2.2 g (92 mg-atoms) of magnesium turnings, and 20 mL of THF produced higher yields of **9**. Unfortunately, the selective destruction of **9** (vide infra) could not be achieved in THF solution.

A general procedure for the preparation of ether solutions of **9** was ultimately achieved using an adaptation of the method described by Rieke and Bales[14] for preparing Grignard reagents from unreactive organic halides under mild conditions. Thus, into a 250-mL, flame-dried, three-neck flask equipped with a Teflon-coated magnetic stirrer bar and a reflux condenser were placed 9.87 g (104 mmol) of anhydrous magnesium chloride, 5.0 g of sodium–potassium (78% K) alloy, and ether (60 mL). The resulting mixture was refluxed for 96 h during which time the silvery, molten alloy was replaced by a fine, black precipitate. A solution of *exo*-**4** (7.70 g, 38.0 mmol) in ether was added dropwise at room temperature over a 4.5-h period with vigorous stirring. After an additional 1.5 h of stirring at ambient temperature, the reaction mixture was transferred to several flame-dried centrifuge tubes, each of which had been capped with a rubber septum. The reaction solids were compacted by centrifugation and the supernatant liquid transferred by cannula under a positive pressure of nitrogen to an appropriate storage container. The concentration (0.20 M as total base) was determined by titration against standardized 0.10 M HCl. Attempts to prepare higher concentrations of this Grignard in ether were uniformly unsuccessful.

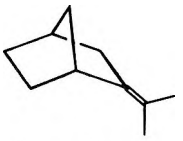
Determination of the Stereochemistry of 9. The epimeric composition of the Grignard reagent **9** in ether was determined by a procedure analogous to that described for 2-norbornylmagnesium bromide. Thus, **9** (8.0 mL, 0.18 M) and methyllithium (2.5 mL, 1.6 M) were added by syringe to a solution of bromo(tri-*n*-butylphosphine)-copper(I) dissolved in 3 mL of ether at −78 °C. The mixture was shaken vigorously for 1 min, then treated with nitrobenzene (1.0 mL) at −78 °C. The resulting mixture was hydrolyzed with concentrated hydrochloric acid (0.10 mL) and centrifuged and the yellow, supernatant liquid passed through a 0.5 × 3 cm column of neutral alumina. The eluent was concentrated and the epimeric mixture of 2,3,3-trimethylnorbornane collected. Reinjection onto a 24 ft × 0.125 in. Hi-Pak SE-30 column (Hewlett-Packard) indicated an epimer composition of 84% endo, 16% exo.

Selective Destruction of *endo*-9. Reaction of 9 with Benzophenone in Ether. An equilibrium mixture of 3,3-dimethyl-2-norbornylmagnesium bromide (8.0 mL, 0.18 M) was injected by syringe into a 40-mL, flame-dried centrifuge tube capped with a rubber septum and containing a Teflon-coated magnetic stirrer bar. The vessel was cooled to −78 °C and with vigorous shaking a solution of benzophenone (0.105 g, 0.589 mmol) in ether (3.0 mL) was added by syringe. The reaction mixture was stirred at ambient temperature for ca. 1 min. The precipitated solids were compacted by centrifugation and the clear red solution transferred by cannula to a clean, flame-dried centrifuge tube and stored at −78 °C until used. Analysis of the stereochemical composition of this material as described above indicated that it contained a 63% endo, 37% exo epimer distribution.

Reaction of *endo*-2-Norbornylmagnesium Bromide with Acetone. Into a 40-mL, flame-dried centrifuge tube capped with a rubber septum and equipped with a Teflon-coated magnetic stirrer bar was transferred by syringe 10 mL (8.0 mmol) of an ether solution of 2-norbornylmagnesium bromide. The vessel was cooled in an ice bath and, with vigorous stirring, anhydrous acetone (1.0 mL) was added dropwise over a 30-min period. The resulting mixture was stirred for an additional 30 min, then cautiously hydrolyzed by the addition of 1.0 mL of a saturated aqueous solution of ammonium chloride. After drying ($MgSO_4$), an additional 5 mL of ether was added and the mixture centrifuged. The clear supernatant solution was removed, concentrated to about one-half its volume, and subjected to GLC analysis. The last and next-to-the-last components to elute were identified, respectively, as the Wurtz-type coupling product 2,2′-bisnorbornane (M^+ 190) and dimethyl(*endo*-2-norbornyl)carbinol (*endo*-**1**, 48%). The IR of *endo*-**1** (CCl_4) exhibited two high-frequency vibrations at 3600 (sh, m) and 3470 cm^{-1} (br, m), characteristic, respectively, of nonassociated and associated ν (O–H). The ^1H NMR spectrum of a sample of *endo*-**1** collected from GLC showed δ (CCl_4) 0.96 (CH_3, s), 1.02 (CH_3, s), 1.09 (OH, s), and 0.80–1.60 (br, multiplet). The appearance of two nonequivalent methyl resonances results from their diastereotropic nature; the assignment of the O–H resonance was confirmed by the substantial dependence of its chemical shift and line width on solvent and concentration. A further analysis of the ^1H NMR spectrum of *endo*-**1** is given in Table I. Elemental analysis was carried out on a collected sample of *endo*-**1**. Anal. Calcd: C, 77.95; H, 11.69. Found: C, 77.90; H, 11.50.

In addition to the aforementioned products, a significant yield of norbornane and norbornene (identified by a comparison of GLC retention times and mass spectra) was also observed.

A further minor component present in an undetermined amount was also isolated by preparative GLC. It had IR (CCl_4) 2890 (C–H), 1440 (m), and 1365 cm^{-1} (m). Its ^1H NMR spectrum revealed δ (CCl_4) 1.20 (s), 1.50 (d, CH_3, J = 1.2 Hz), 1.65 (d, CH_3, J = 2.0 Hz), 2.35 (br, 1 H, bridgehead), 2.85 (br, 1 H, bridgehead), 0.80–2.20 (br, complex). The Raman spectrum of this material (neat) exhibited an intense, sharp band at 1689 cm^{-1}, the position and intensity of which are characteristic of the ν (C=C) observed in tetrasubstituted olefins. A mass spectrum of this compound showed *m/e* (rel intensity) 136 (12, M^+) 121, 107 (100), 93 (63), and 79 (59). Based on these spectroscopic data, this substance is tentatively identified as **11**, produced as a result of the dehydration of **1** during its isolation. The fact that the yield of **11** increases with increasing injection port, column, and detector temperature is consistent with this assignment.



11

Preparation of *endo*-2,2,3-Trimethylnorbornane (15). Authentic **15** was synthesized by the sequence of reactions described below.

***exo*-2-Methylbicyclo[2.2.1]hept-5-ene-*cis,endo*-2,3-dicarboxylic acid (12)** was prepared in 88% yield by the literature procedure[15] (mp 129–130 °C, lit.[15] 122 °C).

exo-2-Methylbicyclo[2.2.1]hepta-*cis,endo*-2,3-dicarbinol (14). Into a 250-mL flask equipped with a Dean-Stark trap was placed 5.0 g (25 mmol) of **12** and 100 mL of benzene. The mixture was refluxed for 24 h and the water that resulted removed periodically. The remaining solution was concentrated to dryness and the residual gummy solid purified by vacuum sublimation (80 °C, 0.1 Torr) to yield 2.3 g (60%) of *exo*-2-methylbicyclo[2.2.1]hept-5-enedicarboxylic anhydride (**12a**), mp 136.5–137.5 °C (sealed capillary). Reduction of **12a** (20 g, 0.10 mol) to *exo*-2-methylbicyclo[2.2.1]hepta-*cis,endo*-2,3-dicarboxylic anhydride (**13**) was achieved in quantitative yield in a Parr apparatus over PtO_2 catalyst suspended in ethyl acetate under a hydrogen atmosphere (40 psi). The catalyst was removed by filtration and the product isolated by concentrating the mother liquor to dryness, mp 134–135 °C.

Compound **13** (23 g, 0.11 mol) was dissolved in 150 mL of dry THF and this solution was placed in a 200-mL addition funnel and added dropwise to a solution of $LiAlH_4$ (26 g) dissolved in 300 mL of THF contained in a 500-mL flask equipped with a Teflon-coated stirrer. The flask was cooled to 0 °C and the reaction mixture stirred vigorously throughout the course of addition. The resulting mixture was subsequently refluxed (under nitrogen) for 7 days before destroying the excess $LiAlH_4$ by the cautious addition of ethyl acetate accompanied by cooling and stirring. Methanol was cautiously added until the evolution of gas subsided. The resulting thick paste was treated with 500 mL of 10% H_2SO_4 and the mixture extracted with five 300-mL portions of ether. The combined extracts were washed with 10% aqueous K_2CO_3, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was subjected to a short-path distillation. The product, bp 116–120 °C (0.1 Torr), is a low-melting, gummy solid [IR (CCl_4) 3400 cm^{-1} (vs)] and is assigned the structure **14**. The isolated yield is 83%.

The ditosylate of the diol 14 was prepared by dissolving 15 g (90 mmol) of **14** in 20 mL of dry pyridine contained in a 250-mL flask. To this solution was added dropwise at 0 °C a solution of 49 g (0.26 mol) of *p*-toluenesulfonyl chloride dissolved in 50 mL of pyridine. A white solid soon appeared. The addition completed, the mixture was allowed to warm to room temperature and stir overnight, then treated with 50 mL of ice-cold water followed by 80 mL of ice-cold concentrated HCl. The resulting mixture was extracted with four 200-mL portions of CH_2Cl_2. The combined extracts were washed with 200 mL of a saturated aqueous solution of K_2CO_3, dried ($MgSO_4$), and concentrated to dryness under reduced pressure. The resulting oil was dissolved in a minimal amount of warm benzene. This solution was treated with petroleum ether until almost cloudy and placed in a refrigerator for 3 days. The white solid that formed was collected by suction filtration, air dried, and used directly in the next reaction.

Reduction of the Ditosylate of 14 with $LiAlH_4$. The crude tosylate obtained above (3.0 g) was dissolved in 20 mL of THF. This so-

lution was then added dropwise to a suspension of 0.5 g of $LiAlH_4$ in 50 mL of THF contained in a 100-mL flask. Vigorous stirring and cooling (0 °C) were maintained throughout the addition. The resulting mixture was refluxed for 24 h. The residual $LiAlH_4$ was cautiously destroyed and the reaction mixture poured into ice water and extracted with three 50-mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated on a steam bath. GLC analysis on a 24 ft × 0.125 in. Hi-Pak SE-30 indicated two components in a 5:95 ratio (in order of increasing retention times). These peaks had identical retention times with those of the two components obtained from the reduction of camphene with hydrogen, the observed ratio in this instance being (in order of increasing retention times) 28:72. The latter peak to elute is, therefore, assigned as *endo*-2,2,3-trimethylnorbornane (**15**), and the former peak as *exo*-2,2,3-trimethylnorbornane.

Preparation of Authentic *exo*-1 and *endo*-1. *exo*-2-Norbornanecarboxylic acid[16] was converted to the corresponding acid chloride [bp 80–81 °C (10 Torr), lit.[17] 84 °C (15 Torr)] by treatment with thionyl chloride.

exo-2-Norbornanecarboxylic acid chloride (12.2 g, 77.0 mmol) was placed in a 1-L, three-necked, flame-dried flask equipped with an addition funnel, reflux condenser, and Teflon-coated magnetic stirrer bar. Dry ether (200 mL) was added. The addition funnel was charged with 200 mL (0.260 mol) of a solution of methyllithium in ether, which was added under a static head of nitrogen at a rate sufficient to maintain a gentle reflux. At the completion of addition the resulting mixture was refluxed for 45 min, then cautiously hydrolyzed with 50 mL of water followed by 50 mL of 6 M HCl. The layers were separated, and the aqueous layer extracted with three 125-mL portions of ether. The combined organic layers were washed with 250 mL of a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give 12.4 g of a dark brown, viscous oil. This material was subjected to chromatography through a 2.3 × 48.5 cm column of alumina (neutral, Fischer chromatography grade). Elution was achieved by treatment with 200 mL of petroleum ether followed by elution with 200 mL of a 1:9 (v/v) mixture of diethyl ether–petroleum ether and finally by 200 mL of diethyl ether. The material of interest eluted with the diethyl ether containing fractions. These were collected and concentrated under reduced pressure. The residual viscous oil (5.6 g) was distilled [bp 93–95 °C (13 Torr)] to give 3.8 g (32%) of material with the empirical formula $C_{10}H_{18}O$: IR (neat) 3450 (br, OH), 2940 cm^{-1}.

The ^1H NMR spectrum of this material in CCl_4, observed in the presence of the shift-inducing reagent $Eu(fod)_3$, revealed two isomers, one of which moved considerably more rapidly downfield than the other upon sequential addition of $Eu(fod)_3$. A comparison of these spectra with that of the *endo*-1 isolated from the reaction of norbornylmagnesium bromide with acetone established that one component was in fact *endo*-**1**, which we conclude formed as a result of epimerization in the course of the reaction of exo-2-norbornanecarboxylic acid chloride with methyllithium. The remaining component is, by exclusion, assigned the structure *exo*-**1**. Component analysis can also be achieved on 24 ft × 0.125 in. Hi-Pak Carbowax column (Hewlett-Packard). Under these conditions the endo isomer elutes first.

Registry No.—*endo*-**1**, 61723-39-5; *exo*-**1**, 61723-40-8; *endo*-**3**, 13058-87-2; **4**, 61723-41-9; **7**, 640-54-0; **8**, 23887-56-1; *endo*-**9**, 61723-42-0; *exo*-**9**, 61723-43-1; **11**, 4696-14-4; **12**, 28871-71-8; **12a**, 18310-60-6; **13**, 1873-09-2; **14**, 18310-62-8; **14** ditosylate, 61723-44-2; *p*-toluenesulfonyl chloride, 98-59-9; acetone, 67-64-1; *exo*-2-norbornanecarboxylic acid chloride, 1195-11-5.

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(12) (a) The reaction of 2-norbornylmagnesium bromide with formaldehyde has been examined by D. E. Bergbreiter and O. M. Reichert, *J. Organomet. Chem.*, submitted. We thank Professor Bergbreiter for a preprint of this manuscript. (b) For a discussion of the stereochemical consequences of electrophilic substitution of Grignard reagents (specifically, carbonation, bromomercuration, and deuterolysis) see G. R. Buske and W. T. Ford, *J. Org. Chem.*, **41**, 1998 (1976); H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **86**, 3288 (1964); H. M. Walborsky and M. S. Aronoff, *J. Organomet. Chem.*, **51**, 31 (1973); G. J. Martin and M. L. Martin, *Bull. Soc. Chim. Fr.*, 1636 (1966); T. Yoshino and Y. Manabe, *J. Am. Chem. Soc.*, **85**, 2860 (1963); T. Yoshino, Y. Manabe, and Y. Kikuchi, *ibid.*, **86**, 4670 (1964); also ref 4.
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Reduction of Some 7-Norbornenols with Lithium Aluminum Hydride–Aluminum Chloride

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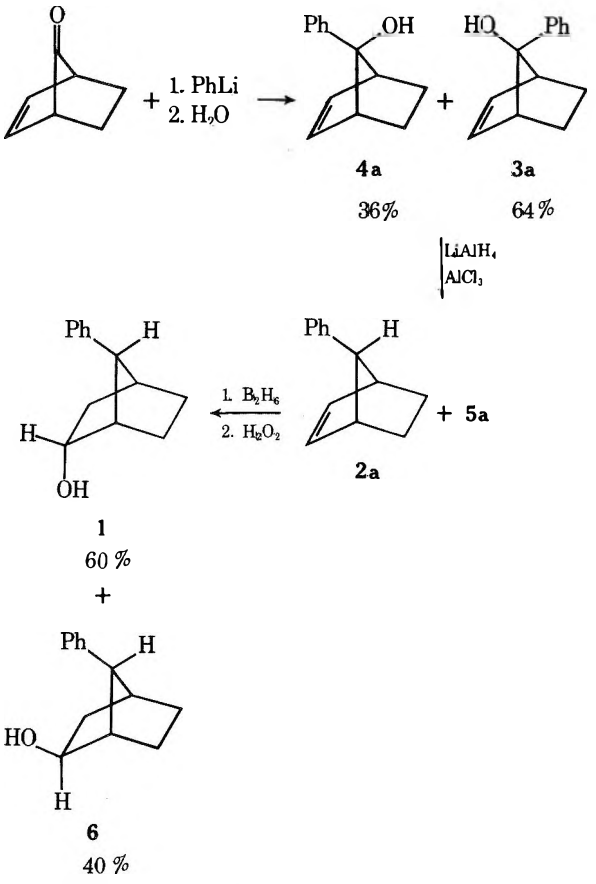
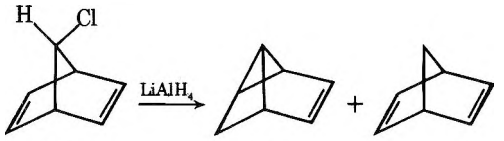
Reduction of a mixture of 7-phenyl-7-norbornenols with $LiAlH_4$–$AlCl_3$ gave 7-*syn*-phenylnorbornene (70%) and 7-phenyltricyclo[4.1.0.$0^{3,7}$]heptane (30%). Tricyclic hydrocarbon with deuterium incorporation exclusively at the endo-2 position was formed when the alcohol mixture reacted with $LiAlD_4$–$AlCl_3$. Reduction of a 7-*p*-anisyl-7-norbornenol mixture afforded 7-*syn*-*p*-anisylnorbornene (62%), 7-*anti*-*p*-anisylnorbornene (32%), and 7-*p*-anisyltricyclo[4.1.0.$0^{3,7}$]heptane (6%). Reduction of 7-*syn*-norbornenol proceeded to 7-norbornanol, whereas 7-*anti*-norbornenol was unaffected by the reduction medium.

In the course of our research on arylnorbornyl derivatives[1] a route to the alcohol 7-*syn*-phenyl-2-*endo*-norbornanol (**1**) was desired. A possible precursor to **1** is the alkene, 7-*syn*-phenylnorbornene (**2a**). Phenyllithium addition to 7-norbornenone gave a 64% *anti*-phenyl:36% *syn*-phenyl ratio of the unsaturated alcohols, **3a** and **4a**, respectively. Treat-

ment of this alcohol mixture with $LiAlH_4$–$AlCl_3$ in ether by the method of Nystrom and Berger[2] afforded the desired alkene (70%) and an isomeric hydrocarbon, **5a**, whose NMR spectrum showed it to be devoid of unsaturation. Hydroboration of this hydrocarbon mixture gave **1**, its epimeric alcohol (**6**), and unreacted **5a**.



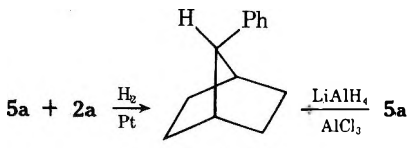
Story[3] found that lithium aluminum hydride reduction of 7-chloronorbornadiene (**7**) produced tricyclo[4.1.0.$0^{3,7}$]heptene-4 (**8**) as one of the reaction products. He proposed that



7 **8**

this tricyclic hydrocarbon resulted from double bond participation. Aluminum hydride coordination with the chlorine should provide a driving force for ionization, which could in turn be assisted by the proper double bond to give a nonclassical intermediate. Because all prior reactions of 7-substituted norbornadienes involved equilibrium processes, no rearrangement products were observed. However, a hydride reduction is presumably irreversible and attack at any carbon atom other than C-7 will afford a rearrangement product. Subsequent to Story's work other investigators have performed reductions upon 2- and 7-substituted norbornenes and have obtained analogous tricyclic products.[4]

Structural Assignment of 5a. Utilizing the aforementioned precedents, it was presumed that $LiAlH_4$–$AlCl_3$ reduction of **3a** and **4a** led to the tricyclic hydrocarbon 7-phenyltricyclo[4.1.0.$0^{3,7}$]heptane as the minor product (30%). Hydrogenations of 8 and tricyclo[4.1.0.$0^{3,7}$]heptane are known to give norbornane as the major product. Similarly, both platinum oxide catalyzed hydrogenation of **5a** and prolonged exposure of **5a** to the $LiAlH_4$–$AlCl_3$ reduction medium gave 7-phenylnorbornane (**9**).



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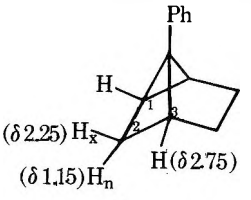
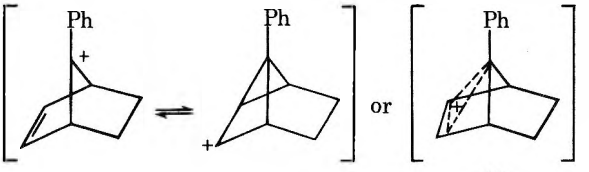
Final confirmation of the structure of **5a** was obtained by detailed analysis of its NMR spectrum. The endo-2 proton of **5a** appears at δ 1.15 as a pair of doublets with $J_{2n,2x}$ = 9.5 and



5a

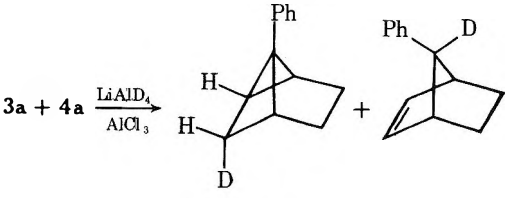
$J_{2n,3}$ = 0.8 Hz, and the exo-2 proton comes at δ 2.75 as a multiplet with $J_{1,2x}$ = 3.5, $J_{2x,3}$ = 7.5 Hz, in addition to the geminal 2x, 2n coupling. A broad doublet at δ 2.75 is assigned to the 3 proton. Spin decoupling experiments were carried out to substantiate these spectral assignments. Irradiation at δ 2.75 removed the small vicinal coupling of 0.8 Hz due to $J_{2n,3}$. In addition, the signal at δ 2.25 collapsed to a doublet pair because the coupling of H-3 with H-2x was removed. Irradiation at δ 1.15 caused the signal at δ 2.25 to collapse to a doublet pair and simplified the broad doublet at δ 2.75 to a pair of triplets, due to $J_{3,4x} = J_{3,4n}$ = 2.3 Hz and $J_{2n,3}$ = 7.5 Hz. Finally, irradiation at δ 2.25 caused a collapse of the endo-2 proton signal at δ 1.15 to a narrow doublet ($J_{2n,3}$ = 0.8 Hz). The coupling constants, $J_{1,2x}$ and $J_{2x,3}$, obtained in this research are similar to those reported by others for analogous tricyclenes.[5]

Mechanistic Considerations. As mentioned earlier in this paper, reduction of both **3a** and **4a** gave the same products. The intermediates presumably formed from these alcohols that could explain how these products were obtained are the equilibrating classical ions, **10** and **11**, and the bridged ion **12**.



10 **11** **12**

In either case, anti-7 hydride attack and endo-2 hydride attack would give the products 2 and **5a**, respectively. To substantiate further the NMR proton assignments of **5a** and to determine the mode of hydride attack at C-2, a mixture of **3a** and **4a** was reduced with $LiAlD_4$–$AlCl_3$. The reaction afforded the deuterated analogues shown below. The formation of **13** with



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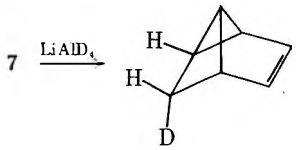
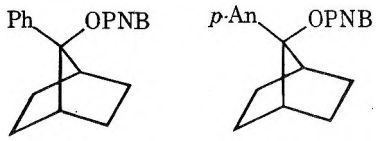
deuterium incorporation exclusively at the endo-2 position is analogous to the results of Story[3] shown in the following equation.

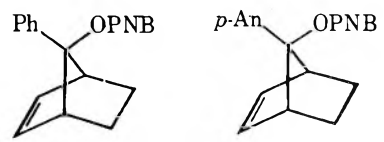


The NMR spectrum of the deuterated tricyclic hydrocarbon (**13**) showed that the absorption at δ 1.15 in **5a** due to the endo-2 proton had vanished.

Driving Force for Double Bond Participation. Relative rate comparisons have served as a means of measuring the amount of double bond participation in solvolysis reactions. Winstein[6] first noted that 7-*anti*-norbornenyl tosylate has a rate which is ca. 10^{11} times faster than that of the saturated analogue, 7-norbornyl tosylate. Using a series of tertiary *p*-nitrobenzoates, Gassman[7] showed that the extent of double bond participation depends on the nature of the nonsolvolyzing 7 substituent. A comparison of the relative solvolysis rates of the 7-aryl-substituted *p*-nitrobenzoates (Ar = Ph vs. Ar = *p*-An) showed a markedly smaller difference, 1 vs. 121, in the unsaturated series as compared with that of the saturated series, 1 vs. 1500.



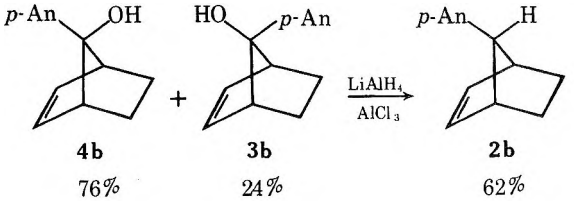
k_{rel} = 1.0 k_{rel} = 1500



k_{rel} = 1.0 k_{rel} = 121

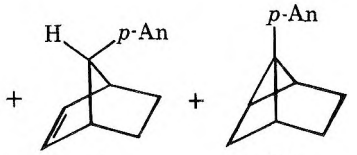
The relatively smaller rate increase observed for the unsaturated series suggests that a smaller driving force for double bond participation operates in the *p*-anisyl case; i.e., the *p*-anisyl substituent stabilizes the tertiary cationic intermediate sufficiently so that less assistance from the π bond is required.[8] Gassman[9] further substantiated the difference in degree of double bond participation from his analysis of the products of the solvolysis reactions. The cation formed from the 7-phenylnorbornenyl *p*-nitrobenzoate suffered attack by solvent exclusively from the anti direction to give 100% of the 7-*syn*-phenyl product. However, the cation formed from the 7-*p*-anisylnorbornenyl derivative gave 8% of solvent attack from the syn direction to give 7-*anti*-*p*-anisyl product. This loss of stereospecificity in the solvolysis products was attributed to some classical ion formation in the *p*-anisyl case, indicative of a smaller driving force for double bond participation.

With Gassman's data as a precedent, we decided to reduce the 7-*p*-anisyl-7-norbornenols with $LiAlH_4$–$AlCl_3$ to determine whether the reduction products would indicate less double bond assistance than the phenyl analogues. Reduction was carried out on a 24% *anti*-*p*-anisyl (**3b**): 76% *syn*-*p*-anisyl (**4b**) mixture of the alcohols. The results of this reaction are summarized below.



4b **3b** **2b**

76% 24% 62%



14 **5b**

32% 6%

Integration of the δ 5.80 and 6.10 signals ascribed to the *syn*-*p*-anisyl and *anti*-*p*-anisyl substituted alkenes, **2b** and **14**, respectively, in the NMR spectrum of the products gave the indicated percentages. The approximate 6% of 7-*p*-anisyltricyclo[4.1.0.$0^{3,7}$]heptane (**5b**) was determined after hydroboration of **2b** and **14**. The formation of product (32%) of syn hydride attack of the 7-arylnorbornenyl cation demonstrates a decrease in the necessity for π bond stabilization of the cation, which is more dramatic than that displayed by Gassman's *p*-nitrobenzoates. The fivefold reduction (6% vs. 30%) in the amount of tricyclic hydrocarbon formed in the *p*-anisyl system serves as just another measure of this decrease.

Because our work up to this point involved only tertiary systems, it was desired to extend the reduction reaction to secondary systems as well. Consequently, both 7-*syn*-norbornenol and 7-*anti*-norbornenol were treated with $LiAlH_4$–$AlCl_3$. Reduction of 7-*syn*-norbornenol gave neither norbornene nor tricyclo[4.1.0.$0^{3,7}$]heptane but only 7-norbornanol. Evidently, the $LiAlH_4$ complexes with the hydroxyl oxygen, a process that facilitates reduction of the double bond. This result is analogous to that of Franzus,[11] who reported that 7-*syn*-norbornenol is reduced by $LiAlH_4$ in ether solvent to 7-norbornanol. If double bond participation were possible in reduction of the secondary systems, 7-*anti*-norbornenol might be the precursor of choice from which to expect the formation of norbornene and tricyclo[4.1.0.$0^{3,7}$]heptane. However, treatment of 7-*anti*-norbornenol with $LAlH_4$–$AlCl_3$ resulted in essentially a quantitative recovery of starting alcohol. Evidently the reaction medium is not conducive to the formation of carbonium ions from secondary 7-norbornenols.

Experimental Section

Melting points were determined in soft capillary tubes using a Hoover capillary melting point apparatus (Arthur H. Thomas Co., Philadelphia, Pa.) and are uncorrected. NMR spectra were obtained with a Varian A-60 or a Varian HA-100 spectrometer. Infrared spectra in the 3-μ region were recorded on a Perkin-Elmer Model 257 grating spectrometer calibrated against polystyrene standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E recording mass spectrometer. The microanalysis was carried out by F. B. Strauss Microanalytical Laboratory, Oxford, England. All ether and ligroin solutions of products were dried over anhydrous sodium sulfate prior to removal of solvent. Ligroin was distilled over potassium permanganate and had bp 40–55 °C.

7-*anti*-Phenyl-7-norbornenol (3a) and 7-*syn*-Phenyl-7-norbornenol (4a). To an ether solution of phenyllithium, prepared from lithium wire (0.98 g, 0.14 mol) and bromobenzene (10.9 g, 0.0694 mol), was added an ether solution of 7-norbornenone (5.00 g, 0.0463 mol), prepared by the method of Gassman and Pape.[12] Reflux was maintained for 3 h, water was added, and the ether solution was evaporated. Distillation of the residual yellow oil in vacuo gave 6.91 g (80.2%) of a colorless oil, bp 105–110 °C (0.10 mm). The integrated NMR spectrum in the region of the signals at δ 6.10 and 5.80 indicated the mixture to be composed of 64% **3a** and 36% **4a**.

Partial separation of **3a** from the mixture could be obtained by crystallization of **3a** from ligroin and by chromatography over F-20 alumina, **3a** being eluted first with ligroin–ether eluent. Pure **3a** gave mp 60–61 °C. The IR spectrum of **3a** (CCl_4) showed O–H absorption at 3619 (free) and 3563 cm^{-1} (O–H—π bond), whereas the spectrum of **4a**, an oil, showed only the free O–H absorption at 3619 cm^{-1}. (See footnote 13.)

7-*syn*-Phenylnorbornene (2a) and 7-Phenyltricyclo[4.1.0.$0^{3,7}$]heptane (5a). An ether solution of $AlCl_3$ (11.7 g, 0.0877 mol) was added to a stirred solution of the 7-phenyl-7-norbornenols (15.0 g, 0.0805 mol). The reaction solution turned a deep wine red color; this solution was added rapidly to an ether solution of $AlCl_3$ (11.7 g, 0.0877 mol) which had been added dropwise into $LiAlH_4$ (8.1 g, 0.17 mol). After about one-half of the wine-colored solution had been added, salts began to precipitate and the color disappeared. The resulting mixture was refluxed for 12 h and cooled, after which water was added cautiously to hydrolyze the addition compound and to destroy excess $AlCl_3$ and $LiAlH_4$. The ether layer was decanted, and the aqueous layer was extracted with ether. The combined ether layers were flash evaporated, leaving a light yellow oil, 13.1 g (96.5%) of a

70%:30% mixture of **2a** and **5a**. (Distillation in vacuo is accomplished with partial decomposition.) In the NMR spectrum (CCl_4), the absorptions at δ 5.80 (2 olefin H), 3.00 (H-1 and H-4), and 2.82 (H-7a) are assigned to **2a**. The signal at δ 2.75, overlapped by the H-7a signal of **2a**, is assigned to **5a**. Integration of these signals allowed the indicated percentages of **2a** and **5a** to be calculated.

The mixture of **2a** and **5a** was hydroborated by the method of Brown and Zweifel.[14] (The experimental details concerning this reaction and the isolation of 7-*syn*-phenyl-2-*exo*-norbornanol (**6**) and 7-*syn*-phenyl-2-*endo*-norbornanol (**1**) have been reported elsewhere.[15]) Chromatography on F-20 alumina with ligroin as eluent gave pure **5a** before any of the alcohols were eluted with ligroin–ether mixtures. Pertinent NMR assignments of **5a** are discussed in the text. The mass spectrum showed the parent peak at *m/e* 170, rel intensity 11.0 compared to the base peak (100.0) at *m/e* 142. Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.58; H, 8.11.

7-Phenylnorbornane (9). A mixture of **2a** and **5a** (1.0 g, 0.0059 mol) in 15 mL of 95% ethanol and 22 mg of platinum oxide was subjected to a hydrogen pressure of 40 psi in a Parr bomb apparatus for 1 h. Filtration of the catalyst and flash evaporation of the solvent left pure **9**, 0.58 g (57%), as an oil: NMR (CCl_4) δ 7.18 (5 H, Ar H's), 2.80 (1 H, H-7), 2.50 (2 H, H-1 and H-4), 1.05–1.75 (8 H, exo and endo protons); mass spectrum showed the parent peak at *m/e* 172, rel intensity 73.9 compared to the base peak (100.0) at *m/e* 104. Hydrogenation of a sample of pure **5a** by the same procedure gave product with an identical NMR spectrum. These NMR spectra were identical with that taken on the product obtained from catalytic hydrogenation of 7-phenylnorbornadiene (Frinton Laboratories).

A pure sample of **5a** was refluxed with an ether solution of $AlCl_3$ and $LiAlH_4$ for 21 h. Hydrolysis and workup as described under the preparation of **2a** and **5a** gave a mixture of unreacted **5a** and **9** (δ 2.80 signal became evident). Repetition of this experiment caused a further increase in the δ 2.80 signal.

2-*endo*-Deuterio-7-phenyltricyclo[4.1.0.0^{3,7}]heptane (13) and 7-*anti*-Deuterio-7-*syn*-phenylnorbornene. A mixture of **3a** and **4a** (3.01 g, 0.0162 mol) was reduced with 2.34 g of $AlCl_3$ and 1.70 g of $LiAlD_4$ by a procedure similar to that described for the preparation of **2a** and **5a**. Workup gave 2.72 g (97.5%) of an approximate 69:31 mixture of 7-*anti*-deuterio-7-*syn*-phenylnorbornene and **13**, as obtained by NMR analysis. No signal at δ 2.80 was observed, indicative of deuterium incorporation at the 7-anti position.

The mixture of 7-*anti*-deuterio-7-*syn*-phenylnorbornene and **13** was hydroborated as described previously.[15] From the mixture (5.58 g, 0.0324 mol), 1.55 g of $NaBH_4$, and 5.60 g of boron trifluoride etherate there was obtained 5.40 g of a mixture of **13** and the 7-*anti*-deuterio analogues of **1** and **6**. Alumina chromatography yielded a pure sample of **13**. The NMR spectrum showed no signal at δ 1.15, indicative of deuterium incorporation at the endo-2 position.

7-*anti*-*p*-Anisyl-7-norbornenol (3b) and 7-*syn*-*p*-Anisyl-7-norbornenol (4b). To an ether solution of *p*-anisylmagnesium bromide, prepared from magnesium turnings (0.35 g, 0.014 mol) and *p*-bromoanisole (2.6 g, 0.014 mol), was added an ether solution of 7-norbornenone (1.0 g, 0.0092 mol). Reflux was maintained for 2 h, water was added, and the ether solution was flash evaporated, leaving 1.2 g of impure yellow oil. The integrated NMR spectrum in the region of the signals at δ 6.10 and 5.80 indicated the mixture to be composed of 24% **3b** and 76% **4b**.[15] Chromatography on F-20 alumina gave 0.89 g (45%) of a pure mixture of **3b** and **4b**. No complete separation of **3b** or **4b** from the mixture was attained.

7-*syn*-*p*-Anisylnorbornene (2b), 7-*anti*-*p*-Anisylnorbornene (14), and 7-*p*-Anisyltricyclo[4.1.0.0^{3,7}]heptane (5b). The reaction was carried out in a manner similar to that used for the preparation of **2a** and **5a**. From the 7-*p*-anisyl-7-norbornenols (0.89 g, 0.0041 mol), 1.40 g of $AlCl_3$, and 0.48 g of $LiAlH_4$ there was obtained 0.54 g (65%) of a mixture of **2b**, **14**, and **5b**. The ratio of **2b** to **14** was obtained by integration of the signals at δ 5.80 and 6.10 in the NMR spectrum. The amount of **5b** could not be determined accurately at this point because apparently only a very small amount was present.

Hydroboration of this mixture using 0.18 g of $NaBH_4$ and 0.55 mL of boron trifluoride etherate gave an oil which was chromatographed on F-20 alumina. With ligroin as eluent there was obtained 0.028 g of a mixture of 7-*p*-anisylnorbornane and **5b**. Because the 7-*p*-anisylnorbornane is presumably formed from **5b** under the reaction conditions, the total weight was attributed to **5b**. The percentages of **2b**, **14**, and **5b** were then calculated to be ca. 62, 32, and 6%, respectively.

Reduction of 7-*syn*-Norbornenol to 7-Norbornanol. The reaction was carried out in a manner similar to that used for the preparation of **2a** and **5a**. From 7-*syn*-norbornenol (5.0 g, 0.045 mol), mp 79–80 °C, prepared by the method of Gerteisen,[17] 13.4 g of $AlCl_3$, and 4.6 g of $LiAlH_4$ there was obtained 2.8 g (56%) of 7-norbornanol, mp 150–151 °C (lit.[11] mp 149–150 °C). The NMR spectrum was identical with that obtained from the platinum oxide catalyzed hydrogenation of 7-*syn*-norbornenol.

Attempted Reduction of 7-*anti*-Norbornenol. Following the procedure used to reduce 7-*syn*-norbornenol to 7-norbornanol, an ether solution of 7-*anti*-norbornenol (2.00 g, 0.0182 mol), mp 115–116 °C (lit.[18] mp 117–118 °C), 3.20 g of $AlCl_3$, and 1.10 g of $LiAlH_4$ was refluxed for 12 h. After the usual workup, 1.53 g (76.5%) of 7-*anti*-norbornenol was recovered. No other compound was found.

Registry No.—**2a**, 29266-12-4; **3a**, 34098-60-7; **3b**, 13143-81-2; **4a**, 34098-58-3; **4b**, 13118-72-4; **5a**, 61675-24-9; **9**, 24892-78-2; phenyllithium, 591-51-5; 7-norbornenone, 694-98-4; $AlCl_3$, 7446-70-0; $LiAlH_4$, 16853-85-3; *p*-anisyl bromide, 104-92-7.

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(1) For the most recent paper in this series, see D. C. Kleinfelter and J. M. Miller, Jr., *J. Org. Chem.*, **38**, 4142 (1973).
(2) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).
(3) P. R. Story, *J. Am. Chem. Soc.*, **83**, 3347 (1961).
(4) For example, see the following: (a) H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, **85**, 2324 (1963); (b) H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **88**, 864 (1966); (c) M. Brookhart, A. Diaz, and S. Winstein, *ibid.*, **88**, 3135 (1966); (d) J. J. Tufariello, T. F. Mich, and R. J. Lorence, *Chem. Commun.*, 1202 (1967).
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(6) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955).
(7) P. G. Gassman and A. F. Fentiman, Jr., *J. Am. Chem. Soc.*, **91**, 1545 (1969).
(8) Another way of presenting this difference is by comparison of the relative rates of solvolysis of the saturated phenyl compound (rel rate = 1.0) vs. the unsaturated analogue and contrasting said comparison with that obtained from the saturated *p*-anisyl compound (rel rate = 1.0) vs. its unsaturated analogue. The 7-phenylnorbornenyl *p*-nitrobenzoate reacts 41 times faster than the saturated 7-phenylnorbornyl derivative, whereas the *p*-anisyl compounds display only an increase of unsaturated compound relative to saturated derivative of 3.4.
(9) P. G. Gassman and A. F. Fentiman, Jr., *J. Am. Chem. Soc.*, **92**, 2549 (1970).
(10) A referee has suggested that **3b** and **4b** (as well as **3a** and **4a**) may not yield the same intermediate (or intermediates). If such were to be the case, then **3b** (and **3a**) must be reacting via a backside hydride displacement. Although our results do not exclude such a possibility, we feel that such a displacement at a tertiary center is unlikely, especially in view of the fact that the secondary alcohol, 7-*syn*-norbornenol, underwent no such displacement reaction.
(11) B. Franzus and E. I. Snyder, *J. Am. Chem. Soc.*, **87**, 3423 (1965).
(12) P. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).
(13) These alcohols, **3a** and **4a**, have been prepared previously (see ref 7), but no physical properties were reported.
(14) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
(15) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, T. E. Dye, and J. H. Long, Jr., *J. Org. Chem.*, **38**, 4127 (1973).
(16) Reaction of phenylmagnesium bromide with 7-norbornenone gave a 24%:76% mixture of **3a** to **4a**.
(17) T. J. Gerteisen and D. C. Kleinfelter, *J. Org. Chem.*, **36**, 3255 (1971).
(18) P. R. Story, *J. Org. Chem.*, **26**, 289 (1961).

Chemistry of Cyclobutene-1,2-dicarbonitrile. 1. Solvolytic and Michael Processes

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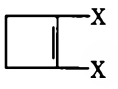
Quenching sulfuric acid solutions of cyclobutene-1,2-dicarbonitrile (1) with water or with methanol yields the diamide 2 and the dimethyl ester 3, respectively, in excellent yields. Prolonged treatment of 1 with dilute sulfuric acid yields the diacid 4. Treatment of 1 with 2-methyl-2-butene in the presence of sulfuric acid gives the Ritter reaction product 5. The dinitrile 1 reacts with secondary amines to give the usual Michael addition products; these undergo facile thermal elimination of hydrogen cyanide to give cyanoenamines, 2-aminocyclobutenecarbonitriles 9 and 10. The latter, upon hydrolysis, give 2-cyanocyclobutanone (12). With basic methanol, 1 yields the expected ethers as minor products, with the major products being imidate esters. The dinitrile 1 undergoes double-bond addition reactions with chlorine and hydrogen chloride; the latter reagent yields secondary products via reaction at the nitrile groups.

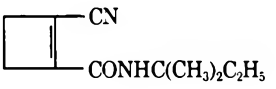
Although the synthesis of cyclobutene-1,2-dicarbonitrile (1) was first reported several years ago,[1] its chemistry has remained virtually unknown. With the recent development of a more convenient synthesis,[2,3] reports concerning the reactions of 1 and related materials have begun to appear.[2,4] For some time we have been investigating the often unique chemistry of this cyclic dinitrile, and wish to report here some of our findings, viz., those concerning solvolysis reactions, ionic additions to the double bond, and processes which involve reactions at both the double bond and nitrile groups.

Dinitrile 1 dissolves immediately in 95% sulfuric acid, giving a colorless solution. On a small scale, this occurs with a modest exotherm; however, on a larger scale (with more than 200 mmol or so of 1), the process may be controlled only by the rather unusual sequence of slow addition of 1 to excess acid with provision for some cooling. Under "normal" conditions (i.e., addition of acid to 1, even slowly and over a prolonged period) on a large scale, after an induction period a strongly exothermic reaction invariably occurred that could not be controlled. Addition of sulfuric acid solutions of 1 to ice water or to methanol afforded excellent yields of cyclobutene-1,2-dicarboxamide (2) and dimethyl cyclobutene-1,2-dicarboxylate (3), respectively. Complete hydrolysis of 1 occurred slowly with hot, dilute (12 N) sulfuric acid, giving cyclobutene-1,2-dicarboxylic acid (4).

It might have been anticipated that the imide would have been formed rather than the diamide 2 in this sequence, and, indeed the imide is formed by a similar treatment of cyclohexene-1,2-dicarbonitrile and *cis,cis*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile.[3] However, the imide in this system, a bicyclo[3.2.0]hept-1[1,5]-ene, is apparently too strained for normal existence.[5] On the other hand, solvolysis of derivatives of *cis*-cyclobutane-1,2-dicarbonitrile does result in the formation of imides.[3] Since the dinitrile 1 is thus incapable of forming an imide, it was possible for a normal Ritter process to occur. Thus, reaction of 1 with 2-methyl-2-butene in 96% sulfuric acid gave *N,N'*-bis(1,1-dimethylpropyl)cyclobutene-1,2-dicarboxamide (5), as well as a little of the cyano amide 6.

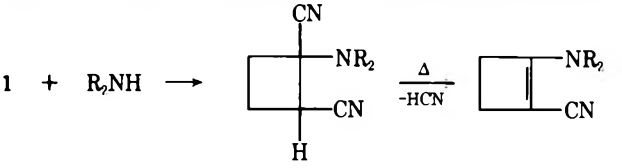


1, X = CN
2, X = $CONH_2$
3, X = CO_2CH_3
4, X = CO_2H
5, X = $CONHC(CH_3)_2C_2H_5$



6

A number of nucleophilic reagents readily add to the double bond system of 1. Since it was found that, e.g., cyclohexene-1,2-dicarbonitrile undergoes no comparable reactions,[3] the reactivity of 1 may be ascribed both to the strong activation of the double bond by the cyano groups and the modest strain present in the cyclobutene system which is relieved upon going to the saturated derivatives. A facile reaction occurred with the secondary amines piperidine and dimethylamine to give the simple adducts 7 and, though not isolated, by analogy, 8, 1-substituted aminocyclobutane-1,2-dicarbonitrile. With piperidine, ^1H NMR monitoring demonstrated that the reaction to 7 was complete within a few hours at room temperature. While the simple adduct 7 (and presumably 8) was reasonably stable at room temperature (vide infra), facile elimination of hydrogen cyanide occurred upon distillation to yield the cyano enamine 9 (and 10), 2-(1-piperidino)cyclobutene-1-carbonitrile. Formation of 9 and 10 was demonstrated by development of an intense enamine absorption in the infrared region at about 1630 cm^{-1} (arising from the strongly polarized double bond) with a concurrent shift of the nitrile absorption to about 2180 cm^{-1}.



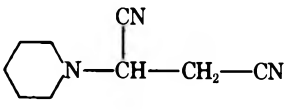
7, R = $-(CH_2)_5-$ 9, R = $-(CH_2)_5-$
8, R = CH_3 10, R = CH_3

In a related system, 3 reportedly underwent smooth addition of diethylamine to give a thermally stable ester analogue of 8.[6] On the other hand, facile elimination processes leading to cyclobutenes related to 9 and 10 have been noted in other work.[7] It is probable that the major determinants in these systems are the presence of a good leaving group (cyanide in the present case, mercaptan in the previous work[7]) and the establishment of a resonance-stabilized, highly dipolar cyano enamine, thus overcoming any reluctance to reestablish the strained cyclobutene system.

To gain further insight into the present elimination process, the relative thermal stability of the acyclic analogue of 7, 2-(1-piperidino)succinonitrile[8] (11), was noted qualitatively. It began to lose hydrogen cyanide at a perceptible rate at about 140–150 °C.[9] In contrast, formation of 9 (or 10) from 7 (or 8) proceeded at 100 °C or less; indeed, 7 exhibited some instability even at room temperature, since stored samples liquefied and developed the odor of hydrogen cyanide.

Although cyano enamines related to 9 and 10 have been available for a number of years,[7,10] the facile preparation described here represents probably the most convenient synthesis for the otherwise unsubstituted cyclobutene cyano

enamines. Very little of the chemistry of **9** or **10** was noted. However, it was found that hydrolysis of **9** under mild conditions gave the elusive[11] 2-cyanocyclobutanone (**12**) (of limited stability), in excellent yields.



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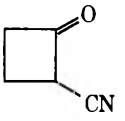
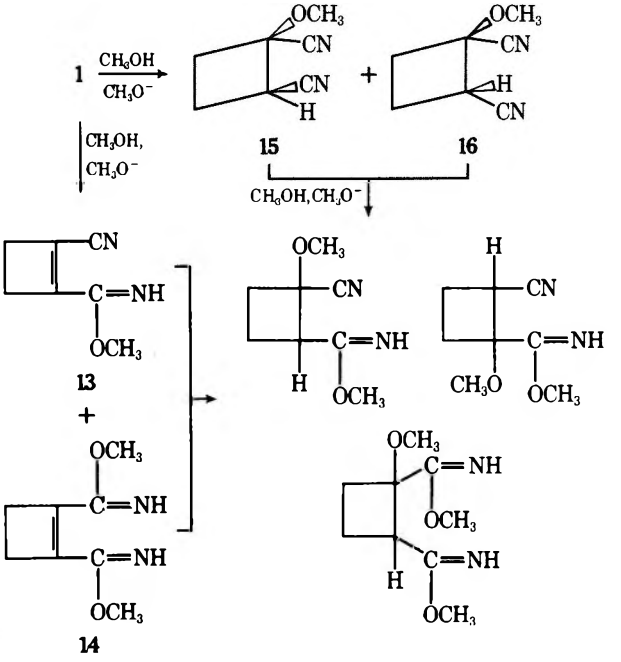


12

In contrast to the straightforward reaction of **1** with secondary amines, condensation with primary amines was more complex.[12] Aniline itself was unreactive. However, *tert*-butylamine and 1,1-dimethylhydrazine did undergo very slow reaction (NMR and VPC monitoring showed that reaction was only 50–60% complete in several weeks), but we were unable to isolate discrete reaction products.

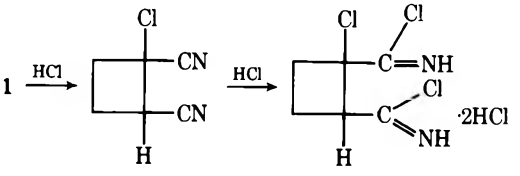
The reaction of **1** with methanol in the presence of sodium methylate or a quaternary ammonium hydroxide was also complex. Products arising from reaction at several positions were observed, i.e., the double bond, one or both of the cyano groups, and all of these positions. The major products were the mono- and diimidate esters **13** and **14**, with small amounts of the simple addition products (*E*)- and (*Z*)-1-methoxycyclobutane-1,2-dicarbonitrile (**15** and **16**) being isolated (earlier workers noted that the ester **3** is inert toward alkoxide[14]). Other products isolated included imidate esters (from spectral data) arising from **15** and **16**, but of otherwise undetermined structure (see Scheme I). Under identical conditions, **1** failed to undergo reaction with *tert*-butyl alcohol.

Scheme I

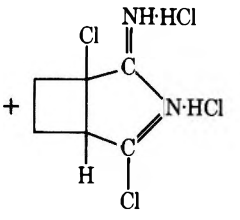


14

Cyclobutene **1** underwent slow reaction with chlorine at room temperature to give a 90:10 mixture of *trans*- and *cis*-1,2-dichlorocyclobutane-1,2-dicarbonitrile.[15] Monitoring the process by VPC demonstrated that this ratio remained constant throughout the reaction period. The addition of hydrogen chloride to **1**, although somewhat faster than chlorine (VPC and NMR indicated complete reaction in a few hours), was complicated by a secondary reaction involving both cyano groups. While no attempt was made to distinguish between them, the (VPC) ratio of the two simple adducts, *cis*- and *trans*-1-chlorocyclobutane-1,2-dicarbonitrile, was about 2:1. As a by-product, an appreciable amount (30–35 wt % yield) of an organic salt (containing no cyano groups) was formed. Analyses of this moisture-sensitive salt were ambiguous, but suggested that formation of imidoyl chlorides such as **17** or **18** might be involved. The product was very soluble (with a strong exotherm) in water, yielding copious amounts of hydrogen chloride and ammonium chloride (about 25 wt %) as the inorganic products.



17



18

Experimental Section[16]

Cyclobutene-1,2-dicarboxamide (2). Sulfuric acid (96%, 75 mL) was stirred in a water bath at ca. 25 °C, maintaining this temperature by the addition of a few pieces of ice as necessary, while 30 g of cyclobutene-1,2-dicarbonitrile (**1**) was added dropwise over a period of 4 h. The pale yellow solution, after being stored at room temperature for a day or so, was poured over 50 g of crushed ice. The resulting white solid was filtered, washed well with cold water, and recrystallized from 1500 mL of boiling water (Norit) to give 26.0 g (65%) of **2**: mp 238 °C dec (ammonia liberated) (lit.[2] mp 250–252 °C); IR (KBr) 3420, 3220, 1680, 1640 cm^{-1}. Anal. Calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.19; H, 5.74; N, 19.80.

Dimethyl Cyclobutene-1,2-dicarboxylate (3). A sulfuric acid solution of **1** (30 g), prepared as in the preparation of **2**, was poured slowly into 1 L of methanol. The solution was heated under reflux for 48 h, and the methanol then removed under aspirator pressure. The residual oil, taken up in ice water, was extracted three times with ether. The combined extracts were washed three times with water, dried over magnesium sulfate, and stripped to give 30 g of a solid. Recrystallization from ether (100 mL) afforded 13.9 g (first crop) of **3** as snow-white crystals: mp 42–43 °C (lit.[2] mp 43.5–44 °C) (further crops of **3** were obtained from the ether filtrate, and by further extraction of the water solution with chloroform, giving a total yield of crystallized **3**, of varying purity, of about 35 g); IR (KBr) 1730 (C=O), 1640 (C=C), 1220 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 55.98; H, 5.66.[17]

Cyclobutene-1,2-dicarboxylic Acid (4). A mixture of 20 g of **1**, 100 mL of water, and 50 mL of 96% sulfuric acid was stirred on a steam bath for 20 h. The resulting hot solution, after treating with Norit, was cooled to give the acid **4** as a white, crystalline solid. The aqueous solution was extracted with methylene chloride. Removal of the solvent from the extracts gave more of the acid **4** (total yield of 8 g). Recrystallization from ether gave **4** as white crystals: mp 176–178 °C (gaseous dec) (lit.[2] mp 183–185 °C); IR (KBr) 2500–3000, 1710, 1590, 1265, 1235 cm^{-1}; ^1H NMR (CF_3COCF_3·D_2O) δ 5.63 (s, CO_2H), 2.82 (CH_2). Anal. Calcd for $C_6H_8O_4$: C, 50.71; H, 4.26. Found: C, 50.65; H, 4.08.

***N,N'*-Bis(1,1-dimethylpropyl)cyclobutene-1,2-dicarboxamide (5).** A solution of 5.2 g (0.05 mol) of **1** in 25 mL of acetic acid and 10 mL of 96% sulfuric acid, after being allowed to stand at room temperature for 30 min, was stirred with cooling in a water bath (25–30 °C) while 7.0 g (0.10 mol) of 2-methyl-2-butene was slowly added. After being allowed to stand at room temperature overnight, the solution was poured into ice. The resulting semisolid was extracted into ether, and the ether solution was washed with water, aqueous bicarbonate, and again with water. Removal of the ether gave ca. 8 g of an oil. Recrystallization from hexane gave 5.85 g of a low-melting solid. This was taken up in ether, removing 0.33 g of insoluble **2-cyano-*N*-(1,1-dimethylpropyl)cyclobutene-1-carboxamide (6)**: mp 134–136 °C (from ether); IR (KBr) 3340 (NH), 2230 (CN), 1635, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.6 (broad s, NH, 1), 2.74 (s, ring CH_2, 4),

Table I. Spectral Properties of Methanol Adducts of 1

Adduct	IR, cm^{-1} [a]	NMR, δ [b] ^1H	NMR, δ [b] ^{13}C	Mass spectrum, m/e [c] (rel abundance)
13	3285 (=NH)	3.84 (CH_3, s, 3)	164 (C=N)	136 (100)
	2230 (CN)	2.75 (CH_2, s, 4)	114 (C≡N)	121 (55)
	1650 (C=C)		53.2 (OCH_3)	105 (52)
	1595 (C=N)		28.7 (CH_2)	78 (83)
	1093 (C–O–C)		28.2 (CH_2)	58 (40)
14	3220, 3305 (=NH) [d]	8.18 (NH, 2)	163 (C=N)	Like 13
	1630 (C=C)	3.82 (CH_3, s, 6)	138.1 (C=C)	
	1595, 1600 (C=N)	2.55 (CH_2, s, 4)	52.8 (OCH_3)	
	1095 (C–O–C)		26.2 (CH_2)	
15	2280 (CN)	3.65 (CH, m, 1)		136 (0.4)
	1150 (ether)	3.54 (CH_3, s, 3)		108 (72)
		2.54 (CH_2, m, 4)		83 (100)
16	2280 (CN)	3.47 (CH_3, s, 3)		Like 15
	1150 (ether)	3.3 (CH, m, 1)		
		2.4 (CH_2, m, 4)		

[a] KBr pellet. [b] $CDCl_3$, Me_4Si as internal standard. [c] Major fragmentations only. [d] Became a single peak in CCl_4, 3320 cm^{-1}.

1.80 (quartet, chain CH_2, 2), 1.36 (s, CH_3, 6), 0.86 ppm (t, CH_3, 3). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.58; H, 7.93; N, 13.92.[17]

After removal of insoluble **6**, the ether solution was diluted with hexane and chilled at −70 °C to give 4.80 g of **5**. Recrystallization once from ether and once from a mixture of ether and hexane afforded **5** as off-white crystals: mp 99–101 °C; IR (KBr) 3300 (NH), 1670, 1630, 1590, 1540, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (s, NH, 2), 2.54 (s, ring CH_2, 4), 1.83 (quartet, chain CH_2, 4), 1.37 (s, CH_3, 12), 0.90 (t, CH_3, 6). Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.54; H, 10.06; N, 9.99. Found: C, 68.22; H, 9.56; N, 10.14.

1-(1-Piperidino)cyclobutane-1,2-dicarbonitrile (7). A solution of 10.4 g (0.1 mol) of **1** and 8.5 g (0.1 mol) of piperidine in 10 mL of carbon tetrachloride was allowed to stand under nitrogen in a refrigerator for 3 weeks. The solvent was removed in vacuo, and the residue was taken up in 50 mL of ether, discarding a small amount of insoluble material. Chilling of the ether solution for several days at −70 °C gave **7**, 3.0 g after two recrystallizations from ether in the same manner, as hard, ivory-colored crystals: mp 40–42 °C; IR (KBr) 2270 (CN), 1470, 805 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 3.19 (m, CH, 1), 2.36 (m, CH_2N and ring CH_2, 8), 1.58 (m, CH_2, 6); mass spectrum m/e (rel intensity) 162 (46, M − HCN), 161 (44), 136 (64), 135 (48), 133 (16), 53 (>100), 52 (100) (many others). Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.80; H, 7.99; N, 22.21. Found: C, 69.94; H, 7.47; N, 21.62.[17]

2-(1-Piperidino)cyclobutene-1-carbonitrile (9). A solution of 52 g (0.5 mol) of **1** in 300 mL of chloroform was stirred under nitrogen at 20 °C (water bath) while 42.5 g (0.5 mol) of piperidine in 100 mL of ether was added during 1 h. After the solution was allowed to stand at room temperature overnight and the solvent was removed, the product was distilled in vacuo through a 15-in. Vigreux column to give 4.0 g of unreacted **1** and then 65 g of **9**: bp 125 °C (0.4 mm); IR (neat) 2200 (CN), 1640 (C=C), 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (m, CH_2N, 4), 2.47 (s, ring CH_2, 4), 1.62 (m, CH_2, 6); mass spectrum m/e (rel intensity) 162 (78, M^+), 161 (100), 147 (19), 133 (30), 120 (31), 119 (48) (many others). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.04; H, 8.70; N, 17.26. Found: C, 73.59; H, 9.02; N, 17.08.[17]

2-Dimethylaminocyclobutene-1-carbonitrile (10). A solution of 52.0 g (0.5 mol) of **1** in 300 mL of ether was stirred while 25 g of dimethylamine was added through a gas dispersion tube over a 2–3-h period. The temperature quickly rose to 34 °C, remaining there throughout the remainder of the addition, and the solution rapidly darkened. Analysis (VPC) showed that the reaction was 83% complete when addition of amine was terminated. After the solution was allowed to stand at room temperature overnight, the ether was removed. The residual oil was distilled in vacuo through a 6-in. Vigreux column to give 75 g of a mixture of **8** (CN absorption at 2300 cm^{-1}) and **10**, bp 102 °C (1.5 mm) [lit.[7a] bp 105 °C (4 mm)]; this was redistilled at 10 mm to give **10**. Storage in the refrigerator caused solidification: mp ca. 8 °C; IR (neat) 2180 (CN), 1660 (C=C), 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (s, CH_3, 6), 2.45 (m, CH_2, 4).

2-(1-Piperidino)succinonitrile (11) was prepared by the mixing of ethereal solutions of fumaronitrile and piperidine: mp 83–84 °C (lit.[8] mp 86–87 °C); IR (KBr) 2270 (CN), 1465, 1430, 1110, 895 cm^{-1}.

2-Cyanocyclobutanone (12). A solution of 17.5 g (0.108 mol) of the piperidino cyanoenamine **9** in 50 mL of chloroform was stirred vigorously at room temperature with 50 mL of 6 N hydrochloric acid. The reaction was monitored by VPC and was found to be essentially complete in 1 h. After 3 h, the organic layer was separated, washed twice with water (evaporation of the water solution gave piperidine hydrochloride), and then stripped under aspirator pressure. The residue, 12 g, was taken up in ether, removing 2.0 g of what was probably the hydrochloride of **9**:[18] mp 168–170 °C (from chloroform); IR (KBr) 2130 cm^{-1} (broad, strong, amine HCl). After removal of this insoluble salt, the ether solution was distilled in vacuo through a 6-in. Vigreux column to give 6.0 g of **12** as a colorless oil: bp 67 °C (0.5 mm); IR (neat) 2240 (CN), 1805 (C=O), 1070 cm^{-1}; ^1H NMR (neat) δ 4.32 (complex t, CH, 1), 1.8–3.5 (m, CH_2, 4). Anal. Calcd for C_5H_5NO: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.87; H, 5.39; N, 14.35. This cyano ketone **12** became viscous upon storage, and spectral analyses indicated the presence of nitrile, ketone, and acid groups (at 2240, 1805, and 3400 and 1730 cm^{-1}, respectively). Hydrolysis of the piperidino cyano enamine **9** (16.2 g) in ether (100 mL) with 6 N hydrochloric acid (50 mL) for an extended period showed (by VPC) rapid formation of **12** (100% in ~1 h), and then gradual conversion of this to (probably) cyanobutyric acid and glutaric acid; after 140 h, **12** and these other products were present in 14, 13, and 66% yields, respectively. Workup of the reaction mixture after 140 h afforded about 3.0 g of glutaric acid from each of the two phases: mp 89–99 °C (from ether and pentane); IR (KBr) 2500–3120 (strong, broad), 1730, 915 cm^{-1}; ^1H NMR (acetone-d_6) δ 9.21 (s, CO_2H, 2), 2.2–2.6 (m, CH_2, 4), 1.7–2.0 (m, CH_2, 2).

Reaction of Cyclobutene-1,2-dicarbonitrile with Methanol. A solution of 26 g of **1** in 250 mL of methanol was stirred at 25 °C while a 10% solution of sodium methylate in methanol was added at the rate of ca. 2–3 mL/h for 6 h; VPC monitoring showed that reaction was rapid. After addition of carbon dioxide to "neutralize" the base and filtration of the resultant solid, the methanol solution was stripped under reduced pressure. The residue was taken up in ether, removing an insoluble solid [5.9 g, not investigated further; IR (KBr) 1640, 1470, 1370, 1100, 825 cm^{-1}]. The ether solution was washed several times with saturated salt solution, dried ($MgSO_4$), and distilled through a 6-in. Vigreux column in vacuo to give 26 g of an oil, bp 75–85 °C (0.3 mm). This was redistilled through a spinning band column, giving, as a first cut (reflux ratio of 50:1), an oil, bp 70 °C (0.3 mm), which solidified. Recrystallization twice from ether gave **15** as white crystals, mp 58–59 °C (see Table I for spectral data). Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.19; H, 5.90; N, 19.45.[17] Last fractions from this distillation, bp 77–81 °C (0.4 mm) (about half of the material), were combined and redistilled in the same apparatus at a reflux ratio of 100:1. The first cut was rich in **15** (VPC), while the latter cuts became successively richer in two other major components. These were separated by VPC trapping to give **16** as a pure component (see Table I). Anal. Found: C, 61.36; H, 5.95; N, 20.03. The other component was apparently a mixture of products obtained by addition of 2 equiv of methanol to **1** (see Scheme I); IR (neat) 3340 (NH), 2250 (CN), 1655 (C=O), 1590 (C=N), 1350, 1130 (ether), 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6 (broad s, NH), 3.90 (s, CH_3O), 3.82 (s, CH_3O), 3.56 (s, CH_3O), 3.48 (s, CH_3O), 3.46 (s, CH_3O), 3.33 (s, CH_3O), 3.25 (s, CH_3O), 2.38 (s, CH_2) (in an H ratio of 1:2:3:1:2:1:4:2:13, respectively); mass spectrum m/e (rel intensity) 168 (1.4), 153 (100), 140 (24), 114 (51), 110 (37), 108 (42), 100 (40), 84 (56), 83 (59). Anal. Calcd for

$C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 56.74; H, 7.08; N, 17.05.

In another similar run, the oil obtained after washing the initial ether solution of the product with water was recrystallized from ether at −70 °C to give 4.7 g of white crystals, mp 63–75 °C. Fractional crystallization of this from ether gave **13**, mp 62–63 °C (impure, see below), and **14**, mp 119–119.5 °C, as the more and less soluble components, respectively (see Table I). **14**: Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 56.4; H, 7.1; N, 16.5. **13**: NMR, mass, and IR spectra suggested that the sample contained (about 20%) 14 as an impurity.

1,2-Dichlorocyclobutane-1,2-dicarbonitrile. A solution of 7.1 g (0.1 mol) of chlorine in 150 mL of carbon tetrachloride was stirred at room temperature while 10.4 g of 1 was added slowly. After 16 h, reaction was only ca. 50% complete (VPC); another 10 g of chlorine was added. After another 18 h (VPC showed that reaction was 91% complete), the reaction solution was evaporated. The residual colorless oil, 20 g, was recrystallized from ethanol at −70 °C to give *trans*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, mp 73–75 °C.[19]

Addition of Hydrogen Chloride to Cyclobutene-1,2-dicarbonitrile. A solution of 50 g of 1 in 250 mL of chloroform was stirred under nitrogen with water-bath cooling while hydrogen chloride was introduced slowly. Monitoring by VPC and NMR showed that the reaction was complete in a few hours. After a short time, a white solid began appearing. After 45 h, the mixture was filtered under nitrogen, and the solid was washed well with chloroform and ether (yield 16.7 g): IR (KBr) 3320 (NH), 2670 (~N·HCl?), 1785, 1700 (C=O), 1590 cm^{-1} (C=N). A small sample was recrystallized from a mixture of chloroform and ether at −70 °C (under nitrogen) to give white crystals: mp 200–205 °C; IR (KBr) 2800–3300 (broad, strong, acid?), 1785 and 1700 (imide or anhydride C=O?), ca. 1640, 1168 cm^{-1}. Anal. Found: C, 36.12; H, 3.69; Cl, 35.9; N, 4.13.[21] A small sample of the (unrecrystallized) solid, 2.9 g, dissolved immediately in 3 mL of water, accompanied by a copious evolution of hydrogen chloride and a strong exotherm. After heating for 1 h at 100 °C, cooling gave 0.13 g of ammonium chloride; another 0.60 g of the salt was recovered by addition of isopropyl alcohol and ether to the aqueous filtrate.

After removal of the solid reaction product, the chloroform solution was washed four times with water, dried ($MgSO_4$), and distilled in vacuo through a Claisen head to give 42 g of 1-chlorocyclobutane-1,2-dicarbonitrile, bp 100 °C (0.7 mm).[22]

Registry No.—**1**, 3716-97-0; **2**, 23335-15-1; **3**, 1128-10-5; **4**, 16508-05-7; **5**, 61812-58-6; **6**, 61812-59-7; **7**, 61812-60-0; **9**, 61812-61-1; **9** HCl, 61812-62-2; **10**, 18329-03-8; **11**, 6652-02-4; **12**, 52903-54-5; **13**, 61812-63-3; **14**, 61812-64-4; **15**, 61812-65-5; **16**, 61812-66-6; piperidine, 110-89-4; dimethylamine, 124-40-3; glutaric acid, 110-94-1; methanol, 67-56-1; *trans*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, 52477-39-1; chlorine, 22537-15-1; HCl, 7647-01-0; *cis*-1-chlorocyclobutane-1,2-dicarbonitrile, 61812-67-7; *trans*-1-chlorocyclobutane-1,2-dicarbonitrile, 61812-68-8; *cis*-1,2-dichlorocyclobutane-1,2-dicarbonitrile, 52477-38-0.

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(15) Previous workers isolated only the trans product from the reaction of the diester with bromine.[5]
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(17) While elemental analyses were not entirely satisfactory, these with supporting spectral data clearly established the assigned structure.
(18) Elemental analyses agreed as well as would be expected for the dihydrate of such a moisture-sensitive material. Anal. Calcd for $C_{10}H_{14}N_2$·HCl·$2H_2O$: C, 51.17; H, 8.16; N, 11.93; Cl, 15.10. Found: C, 51.6; H, 7.0; N, 13.7; Cl, 16.2.
(19) This material was identical with authentic *trans*-1,2-cyclobutane-1,2-dicarbonitrile prepared by chlorination of cyclobutane-1,2-dicarbonitrile.[2,3,20]
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(21) These results correspond to an empirical formula of $C_6H_7Cl_2N_{0.5}O_{2.5}$. Anal. Calcd: C, 36.58; H, 3.58; Cl, 35.99; N, 3.55. Partial hydrolysis of the moisture-sensitive salt, perhaps **17** or **18**, introduced oxygen-containing derivatives as impurities.
(22) Identical (by VPC) with material prepared by chlorination of cyclobutane-1,2-dicarbonitrile.[2,3,20]

A Rationalization on the Relative Thermodynamic Stabilities of Fused Five-Membered Tetrahydrofurans with Epimerizable Substitutents. An Anomeric Effect in Furanoses

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A rationalization on the fact that the thermodynamically more stable isomers of fused five-membered tetrahydrofuran derivatives with epimerizable substituents are generally not the expected exo isomers but the endo isomers is proposed. The fact that 2,3-*O*-isopropylidene or benzylidene furanoses exist mainly in the trans-C_1,C_2 configuration should not be explained based on the generally accepted concept that the bicyclo[3.3.0]octane system tends to exist with the fewest possible large endo substituents but should be explained in terms of the anomeric effect.

In this paper, we would like to propose a rationalization on the unexpected fact that the thermodynamically more stable isomers of the fused five-membered tetrahydrofuran derivatives with epimerizable substituents are generally not the exo isomers but the endo isomers.[1] Although the fact was first observed by Ohrui et al.[1] in the field of carbohydrate chemistry, the fact and the rationalization proposed in this paper are believed to be general in organic chemistry.

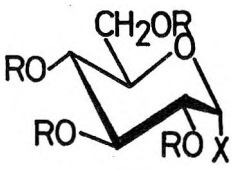

Figure 1.

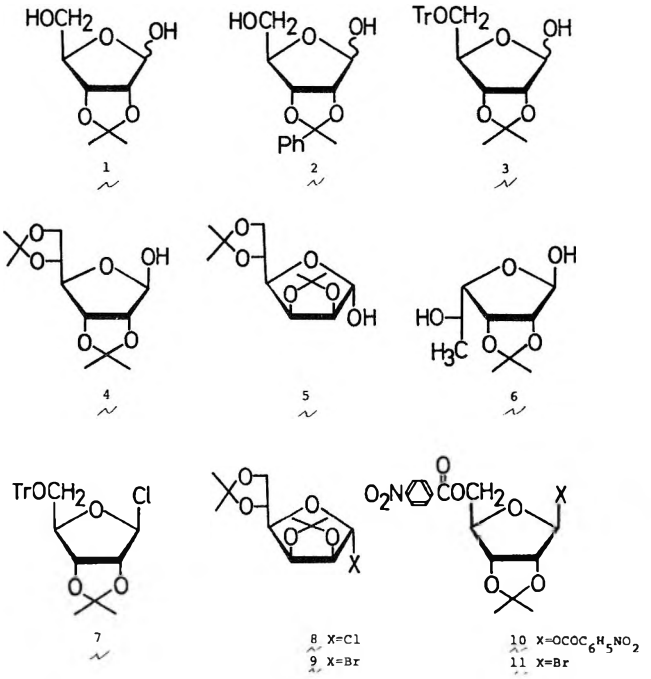

Figure 2.

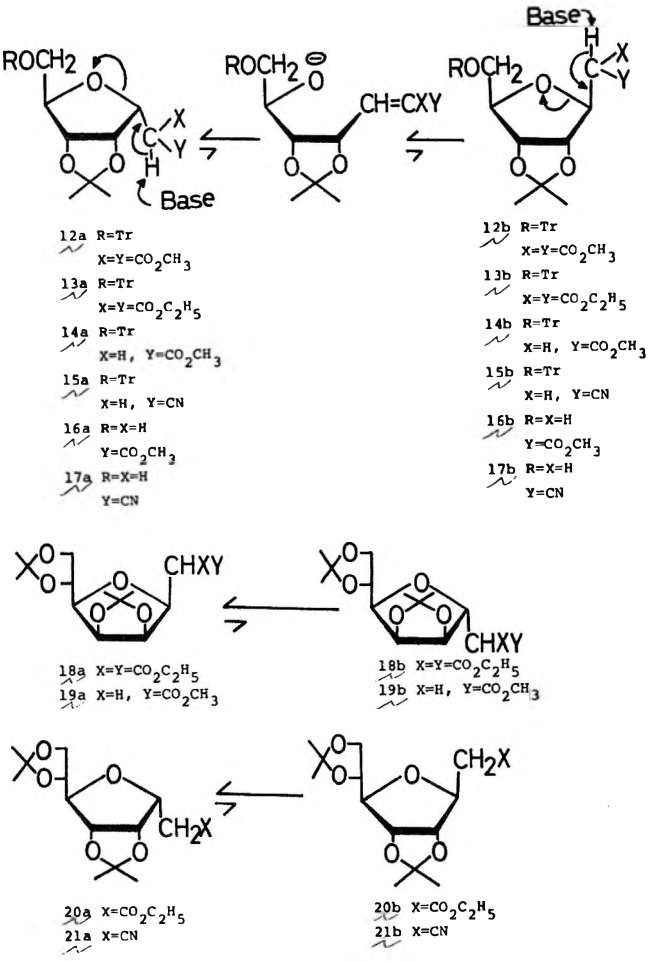

Figure 3.

The anomeric effect[2,3] is a generally recognized phenomenon in the field of conformational analysis of heterocyclic compounds. In carbohydrate chemistry, it is well rationalized by the anomeric effect that such large groups as OR and halides take the axial orientation at the anomeric position of pyranoses. In furanoses, too, several examples of anomeric effect have been reported in the literature.[4-6] However, it is considered that the anomer with a trans-C_1,C_2 relationship is a more favorable configuration in furanoses.[7]

It seems that the trans-C_1,C_2 relationship is the case especially in furanoses of which vicinal 2,3-glycols are protected by forming a 1,3-dioxolane ring. Ample evidences are found in the literature, for example, 2,3-*O*-isopropylidene-D-ribofuranose (**1**)[8], 2,3-*O*-benzylidene-D-ribofuranose (**2**),[8] 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**3**),[1,9a] and 2,3:5,6-di-*O*-isopropylidene-D-allofuranose (**4**)[10] exist primarily in the β form, while 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**5**)[11] and 2,3-*O*-isopropylidene-L-rhamnofuranose (**6**)[11] have the α configuration. The furanosyl chlorides, such as 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**7**)[1,9] and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl chloride (**8**),[12] have been shown to possess the β and α configurations, respectively, in spite of the fact that they are both prepared using reactions that normally proceed with inversion.[13] It is known[14,15] that the treatment of **5** with *N*-bromosuccimide and triphenylphosphine gives the corresponding α bromide (**9**) and the treatment of 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranose (**10**, β:α = 8:1) with hydrogen bromide affords the corresponding β bromide (**11**).

The above trans-C_1,C_2 relationship has been explained by many chemists based on the generally accepted concept that *the bicyclo[3.3.0]octane system tends to exist with the fewest possible large endo substituents.*[16,17]

Very recently, however, Ohrui et al.[1] showed that the base-catalyzed equilibrium of epimerizable 2,3-*O*-isopropylidene-D-furanosyl-*C*-glycosides led to the thermodynamically more stable isomers in which C_1 substituent and the isopropylidene function are in the cis disposition. For example, the base-catalyzed equilibrium of methyl 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl malonate (**12**)[1,9b] gives a 9:1 mixture of methyl 3,6-anhydro-2-deoxy-2-methoxycarbonyl-4,5-*O*-isopropylidene-7-*O*-trityl-D-*altro*-heptonate (**12a**) and -D-*allo*-heptonate (**12b**), through the elimination and recyclization mechanism shown in Figure 3. Many other examples are to be shown; the endo isomers of D-ribofuranosyl *C*-glycosides **13**, **14**, **15**, **16**, and **17**, D-mannofuranosyl *C*-glycosides **18** and **19**, and D-allofuranosyl *C*-glycosides **20** and **21** are thermodynamically more stable than the corresponding exo isomers.

It is clear, therefore, that the generally accepted concept in organic chemistry that *cis fusion of two five-membered rings in the bicyclo[3.3.0]octane system favors the fewest endo substituents is not always the case.*

The factors that makes the endo isomers thermodynamically more stable than the exo isomers in these *C*-glycosyl compounds attracted our attention.

In order to search the forces that stabilize the endo isomers, the conformational analyses of these *C*-glycosyl compounds were undertaken. The chemical shifts and the coupling constants of these *C*-glycosyl compounds are listed in Tables I and II. The ^{1}H NMR spectra of compounds **15a** and **15b** are shown in Figure 4. As can be seen in Table II, the coupling constants of the tetrahydrofuran ring protons of α-D-ribofuranosyl

Table I. 100-MHz Proton Magnetic Resonance Spectra [a]

Compd	Solvent	C_2H	C_2H'	C_3H	C_4H	C_5H	C_6H	C_7H	C_7H'
12a	C_6D_6	4.34 (d)		5.28 (dd)	5.09 (dd)	4.46 (d)	4.27 (m)	3.21 (dd)	3.01 (dd)
12b	C_6D_6	3.85 (d)		4.82 (dd)	4.98 (dd)	4.69 (dd)	4.21 (dt)	3.29 (m)	
13a	C_6D_6	4.29 (d)		5.27 (dd)	5.08 (dd)	4.43 (d)	4.25 (dd)	3.20 (dd)	3.01 (dd)
13b	C_6D_6	ca. 4.0		4.84 (dd)	4.98 (dd)	4.68 (dd)	4.23 (m)	3.32 (m)	
14a	$CDCl_3$	2.75 (d)		4.61 (dt)	4.82 (dd)	4.68 (d)	4.19 (t)	3.27 (dd)	3.09 (dd)
14b	$CDCl_3$	2.62 (dd)	2.78 (dd)	4.31 (dd)	4.63 (dd)	4.55 (dd)	4.13 (ddd)	3.26 (dd)	3.12 (dd)
15a	$CDCl_3$	2.67 (d)		4.50 (dt)	4.79 (dd)	4.71 (d)	4.22 (dd)	3.33 (dd)	3.11 (dd)
15b	$CDCl_3$	2.58 (dd)	2.77 (dd)	4.12 (m)	4.50 (dd)	4.65 (dd)	4.18 (m)	3.33 (dd)	3.21 (dd)
16a	$CDCl_3$	2.72 (d)		4.38 (dt)	4.78 (dd)	4.68 (d)	4.10 (t)	3.60 (d)	
16b	$CDCl_3$	2.56 (dd)	2.74 (dd)	4.24 (ddd)	4.48 (dd)	4.70 (dd)	4.03 (ddd)	3.60 (dd)	3.76 (dd)
17a	$CDCl_3$	2.68 (d)		4.36 (dt)	4.77 (dd)	4.79 (d)	4.16 (dd)	3.65 (m)	
17b	$CDCl_3$	2.67 (dd) [b]	2.85 (dd) [b]	4.10 (m)	4.49 (dd)	4.73 (dd)	4.10 (m)	3.63 (dd) [b]	3.80 (dd) [b]
18a	$CDCl_3$	3.77 (d)		~4.3 (m)	4.90 (dd)	4.74 (dd)	3.51 (dd)	ca. 4.0 (m)	
18b	$CDCl_3$	3.52 (d)		4.60 (d)	4.76 (m)	4.76 (m)		3.8–4.5 (m)	
19a	$CDCl_3$	2.65 (dd)	2.83 (dd)	3.93 (m)	4.76 (m)	4.76 (m)	3.50 (m)	4.38 (ddd)	

[a] Chemical shifts in parts per million from Me_4Si (0), by first-order analysis. [b] After addition of D_2O.

Table II. Coupling Constants (Hz)

Compd	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{6,7'}$	$J_{7,7'}$
12a		10.5		3.5	6	0	3.5	5	10
12b		7.5		4	6.5	4.5	5	5	
13a		10.5		3.5	6	0	3.5	5	10
13b		7.5		3.5	6.5	5			
14a	0	6.5	6.5	4	6	0	4.5	4.5	10
14b	16	6	6	4	6	3.5	4	4.5	10
15a	0	6.5		3.5	6	0	4	4	10.5
15b	16	5.5	7	4.5	6.5	3.5	4	4	10
16	0	7	7	4	6	0	4.5	4.5	
16b	16	5	6.5	4.5	7	4	3.5	3.5	12
17a	0	7	7	4	6	0	4.5	4.5	
17b	16	5	6	5	6.5	3.5	3.5	4.5	12
18a		10		3.5	6	3	7		
18b		9.5		0		3.5	6		
19a	16	6.5					7		
19b	16	7.5		0	6	3.5	7.5		
22a	0	6.5	6.5						0
22b	16	4.5	5	4.5	6	4	4	4	4

Table IIIA. Dihedral Angles Calculated Based on the Karplus Equations. Endo Isomers of D-Ribofuranosyl Derivative

	Hz	Dihedral angle, deg
$J_{3,4}$	3.5–4	45–48 or 129–132
$J_{4,5}$	6	31 or 144
$J_{5,6}$	0	79 or 100

Table IIIB. Dihedral Angles Calculated Based on the Karplus Equations. Exo Isomers of D-Ribofuranosyl Derivative

	Hz	Dihedral angle, deg
$J_{3,4}$	3.5–4	38–48 or 129–138
$J_{4,5}$	6–6.5	27–31 or 144–147
$J_{5,6}$	3.5–4	38–48 or 129–138

C-glycosides (endo isomers) are $J_{3,4}$ = 3.5–4, $J_{4,5}$ = 6, $J_{5,6}$ = 0 Hz (the $J_{3,4}$ corresponds to the $J_{1,2}$ of the furanose ring and so does the $J_{4,5}$ to the $J_{2,3}$ and the $J_{5,6}$ to the $J_{3,4}$) and those of β-D-ribofuranosyl *C*-glycosides (exo isomers) are $J_{3,4}$ = 3.5–5, $J_{4,5}$ = 6–6.5, and $J_{5,6}$ = 3.5–5 Hz. These data indicate that the endo isomers of D-ribofuranosyl *C*-glycosides all exist in very closely related conformations and the same is the case with the exo isomers. The x-ray structure of the endo isomer **22a** is shown in Figure 5. As can be seen in Figure 5, the tetrahydrofuran ring is not the plane but the oxygen atom down envelope form (*Eo*).[7] It seems that the oxygen atom in the tetrahydrofuran ring makes the conformation of the ring fairly flexible and plays the important role in the relative stabilities between the endo and exo isomers. The distances between H_2 and O_2 and between $H_{2'}$ and O_2 in Figure 5 are 2.586 and 2.907 Å, respectively. Therefore, the hydrogen bonding between these atoms is ruled out even in the crystal form.[18] In Figure 5, the cyanomethylene group takes the quasi-equatorial orientation and the interaction by this group is minimized; on the other hand the *p*-bromobenzoyloxy methylene group takes the quasi-axial orientation and there is 1,3-diaxial interaction between this group and H_3. There is almost no change in the ^1H NMR spectra of the endo isomer **15a** in the range of temperature from −50 to 70 °C and this indicates that the conformation of the endo isomer is very rigid and the conformation of compound **22a** shown in Figure 5 will be the same in solution.

Although it is known that the application of the Karplus equations[19] to the five-membered ring might not be appropriate, the conformational analysis of these *C*-glycosyl compounds based on the Karplus equations was next undertaken. The dihedral angles calculated by the Karplus equations

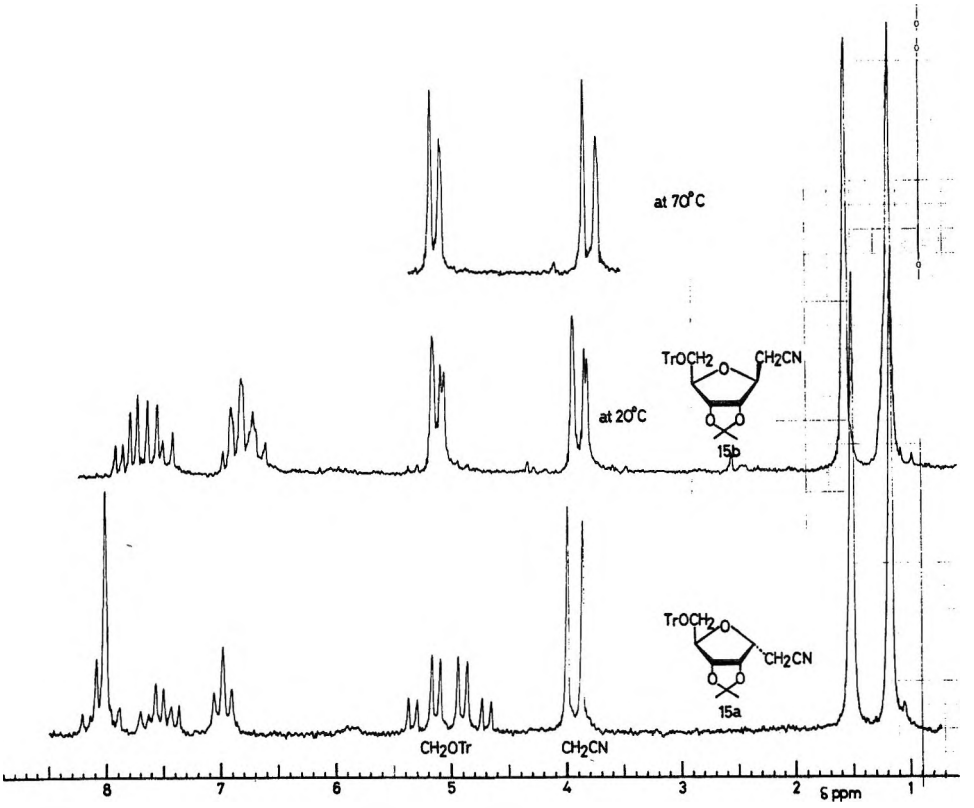

Figure 4. ^{1}H NMR spectra of compounds **15a** and **15b** at 100 MHz in $CDCl_3$.

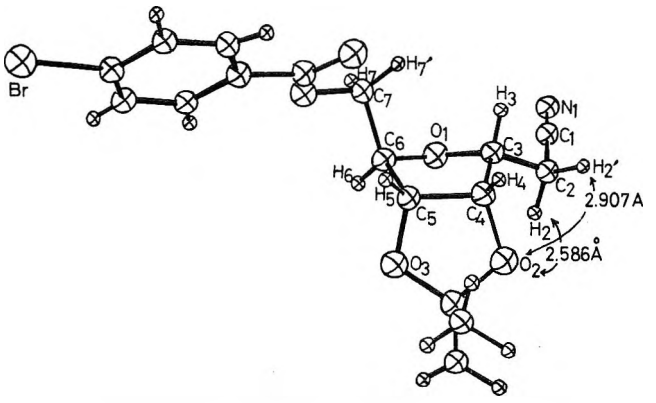

Figure 5. X-ray structure of compound **22a** (endo isomer).

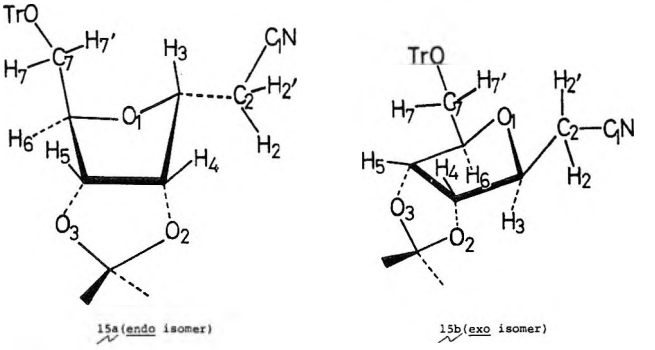

Figure 6.

based on the coupling constants are listed in Tables IIIA and IIIB.

With the help of the Dreiding models and the consideration of steric interactions, the most preferred conformations of both the endo and the exo isomers of D-ribofuranosyl *C*-glycosides are shown using compounds **15a** and **15b,** respectively, in Figure 6. It can been seen that the two conformations of the endo isomers, one based on the x-ray crystallographic method in Figure 5 and another based on the Karplus equations in Figure 6, are both the oxygen atom down envelope form (*Eo*) and resemble each other very well. This indicates that the discussions based on these conformations are very reliable.

In the conformation of the endo isomer **15a** in Figure 6, the cyanomethylene group takes a quasi-equatorial orientation and the cis 1,2- and 1,3-interactions between this group and other atoms are almost relieved. This is consistent with the equivalency (free rotation of C_2–C_3 single bond) of the cyanomethylene protons in the ^{1}H NMR spectrum. Further, in this conformation the cis 1,2-interaction between O_3 and H_6 and the 1,3-interaction between O_2 and H_6 are decreased, since the H_6 takes a quasi-equatorial orientation. On the other hand, the trityloxy methylene group (C_7) takes a quasi-axial orientation. Therefore, there exists the 1,3-diaxial interaction between this group and H_3. This is also consistent with the ABX splitting of the trityloxy methylene protons (H_7 and $H_{7'}$) in the ^{1}H NMR spectrum. In the case of the exo isomers, the conformation is a little twisted oxygen atom up envelope form (°*E*). In this conformation, both the cyanomethylene and the trityloxy methylene group tend to take the quasi-equatorial orientation to decrease the large 1,3-interaction between these groups. Consequently, the H_3 and H_6 are forced to take the quasi-axial orientation and come inside the fused ring system. Therefore, the cis 1,2- and the 1,3-interactions between these protons and the oxygen atoms in the dioxolane ring increase. As the result, the two methylene group cannot take the complete quasi-equatorial orientation and there remain some 1,2- or 1,3-interactions by these methylene groups and the rotation of the C_2–C_3 and C_6–C_7 single bonds is restricted. This is consistent with the ^{1}H NMR spectrum which shows that the two methylene protons are not equivalent at room temperature.

When the instability factors of these two conformations in Figure 6 are compared, there are two O/H cis 1,2-interactions, two O/H 1,3-interactions, and the interaction between the two

Table IV. Final Positional Parameters

Name	G (SD)	X (SD)	Y (SD)	Z (SD)	B (SD)
Br-1	1.00 (0)	0.01904 (27)	0.16811 (9)	0.22336 (4)	
C-15	1.00 (0)	−0.07513 (196)	0.05703 (68)	0.27454 (40)	
C-16	1.00 (0)	−0.27918 (200)	0.00178 (83)	0.26673 (38)	
C-17	1.00 (0)	−0.35097 (210)	−0.07442 (78)	0.30583 (39)	
C-12	1.00 (0)	−0.21709 (171)	−0.09455 (71)	0.35062 (36)	
C-13	1.00 (0)	−0.00316 (245)	−0.03956 (78)	0.35568 (39)	
C-14	1.00 (0)	0.06249 (197)	0.03678 (87)	0.31790 (44)	
C-11	1.00 (0)	−0.29245 (206)	−0.17323 (85)	0.39380 (40)	
O-5	1.00 (0)	−0.16820 (134)	−0.19689 (58)	0.43088 (28)	
O-4	1.00 (0)	−0.51020 (142)	−0.20882 (44)	0.38769 (21)	
C-7	1.00 (0)	−0.59843 (206)	−0.27937 (92)	0.43016 (47)	
C-6	1.00 (0)	−0.63239 (201)	−0.39942 (81)	0.40656 (41)	
C-5	1.00 (0)	−0.40655 (175)	−0.45994 (82)	0.39666 (39)	
C-4	1.00 (0)	−0.37178 (196)	−0.53855 (88)	0.44471 (38)	
C-3	1.00 (0)	−0.57619 (181)	−0.51540 (84)	0.47942 (41)	
O-1	1.00 (0)	−0.75039 (117)	−0.46647 (52)	0.44571 (24)	
O-3	1.00 (0)	−0.43124 (131)	−0.53324 (49)	0.35188 (23)	
C-8	1.00 (0)	−0.33174 (174)	−0.63854 (81)	0.36561 (34)	
O-2	1.00 (0)	−0.37866 (116)	−0.64832 (47)	0.42149 (23)	
C-9	1.00 (0)	−0.46147 (282)	−0.73163 (115)	0.33828 (54)	
C-10	1.00 (0)	−0.07384 (211)	−0.63976 (118)	0.35546 (47)	
C-2	1.00 (0)	−0.67483 (246)	−0.61614 (100)	0.50921)45)	
C-1	1.00 (0)	−0.88965 (271)	−0.58807 (100)	0.53753 (41)	
N-1	1.00 (0)	−1.05160 (221)	−0.56664 (92)	0.56040 (34)	
H-17	1.00 (0)	−0.36907 (1655)	0.01044 (780)	0.23906 (320)	4.00 (0)
H-18	1.00 (0)	−0.47755 (1864)	−0.10890 (744)	0.29829 (314)	4.00 (0)
H-15	1.00 (0)	0.08449 (1739)	−0.06337 (802)	0.38266 (328)	4.00 (0)
H-16	1.00 (0)	0.21583 (1760)	0.07836 (731)	0.32420 (326)	4.00 (0)
H-7	1.00 (0)	−0.49895 (1887)	−0.28116 (654)	0.46399 (296)	4.00 (0)
H-8	1.00 (0)	−0.72373 (1950)	−0.26022 (923)	0.43244 (417)	4.00 (0)
H-6	1.00 (0)	−0.68801 (1725)	−0.40403 (858)	0.37771 (334)	4.00 (0)
H-5	1.00 (0)	−0.28432 (1816)	−0.39881 (852)	0.38843 (349)	4.00 (0)
H-4	1.00 (0)	−0.21437 (1782)	−0.52127 (800)	0.45698 (327)	4.00 (0)
H-3	1.00 (0)	−0.55170 (1824)	−0.46740 (657)	0.50792 (322)	4.00 (0)
H-9	1.00 (0)	−0.38680 (1639)	−0.80607 (752)	0.35062 (305)	4.00 (0)
H-10	1.00 (0)	−0.63316 (2065)	−0.71728 (916)	0.38586 (392)	4.00 (0)
H-11	1.00 (0)	−0.45152 (2062)	−0.71538 (790)	0.30787 (324)	4.00 (0)
H-12	1.00 (0)	−0.03602 (1988)	−0.59870 (724)	0.38143 (313)	4.00 (0)
H-13	1.00 (0)	−0.00246 (2130)	−0.71837 (721)	0.36799 (311)	4.00 (0)
H-14	1.00 (0)	−0.04224 (1899)	−0.62724 (751)	0.32310 (315)	4.00 (0)
H-1	1.00 (0)	−0.56108 (1745)	−0.64192 (721)	0.52979 (313)	4.00 (0)
H-2	1.00 (0)	−0.74587 (1707)	−0.66393 (767)	0.48018 (359)	4.00 (0)

Table V. Final Thermal Parameters

Name	B11 (SD)	B22 (SD)	B33 (SD)	B12 (SD)	B13 (SD)	B23 (SD)
Br-1	7.95 (9)	4.64 (5)	4.50 (5)	−1.89 (7)	1.81 (7)	0.31 (5)
C-15	5.66 (73)	1.95 (38)	3.27 (41)	−0.89 (45)	1.32 (52)	−0.94 (40)
C-16	4.33 (64)	2.53 (41)	3.54 (54)	−1.02 (47)	−0.63 (45)	0.00 (45)
C-17	3.65 (60)	2.34 (48)	3.62 (47)	−0.19 (43)	−0.11 (49)	−1.26 (39)
C-12	1.98 (50)	2.09 (42)	3.40 (46)	−0.02 (40)	−0.17 (41)	−0.21 (38)
C-13	3.46 (61)	2.95 (43)	4.08 (50)	0.29 (60)	0.13 (58)	0.77 (42)
C-14	3.04 (66)	3.95 (53)	4.76 (53)	−0.30 (50)	−0.19 (50)	−0.88 (48)
C-11	4.16 (63)	2.00 (42)	3.84 (51)	0.48 (52)	0.15 (45)	−0.83 (47)
O-5	4.63 (41)	4.33 (40)	4.66 (36)	−0.30 (33)	−0.96 (35)	0.62 (32)
O-4	2.41 (33)	2.72 (28)	4.15 (30)	−0.16 (35)	−0.03 (33)	0.65 (22)
C-7	2.96 (58)	2.89 (46)	4.08 (50)	0.00 (46)	0.87 (49)	0.12 (43)
C-6	3.23 (61)	2.06 (45)	3.03 (46)	−0.44 (43)	0.90 (45)	0.73 (41)
C-5	2.20 (55)	2.41 (44)	3.52 (49)	−0.13 (44)	−0.05 (42)	0.66 (42)
C-4	2.90 (50)	3.42 (49)	3.30 (46)	0.08 (46)	−0.50 (45)	−0.67 (41)
C-3	3.01 (58)	3.47 (49)	3.52 (47)	1.29 (46)	0.49 (47)	−0.47 (41)
O-1	2.88 (31)	3.13 (32)	3.53 (31)	−0.19 (32)	0.20 (30)	0.30 (27)
O-3	5.63 (51)	2.73 (28)	3.64 (29)	0.59 (33)	−0.71 (32)	−0.30 (24)
C-8	3.05 (53)	2.90 (48)	2.97 (43)	0.51 (43)	0.48 (41)	0.23 (37)
O-2	4.77 (37)	2.57 (30)	4.00 (30)	0.43 (30)	1.08 (29)	0.48 (26)
C-9	3.73 (77)	4.04 (57)	5.39 (57)	−0.11 (63)	0.36 (67)	−0.88 (53)
C-10	3.21 (70)	6.08 (68)	4.32 (56)	−0.40 (54)	0.42 (53)	−1.52 (58)
C-2	5.00 (83)	4.33 (65)	4.02 (56)	0.77 (56)	1.05 (54)	1.08 (47)
C-1	6.26 (82)	3.75 (57)	3.04 (55)	0.78 (61)	−0.26 (53)	0.55 (46)
N-1	6.32 (76)	5.16 (51)	4.42 (50)	0.93 (57)	1.15 (56)	1.33 (43)

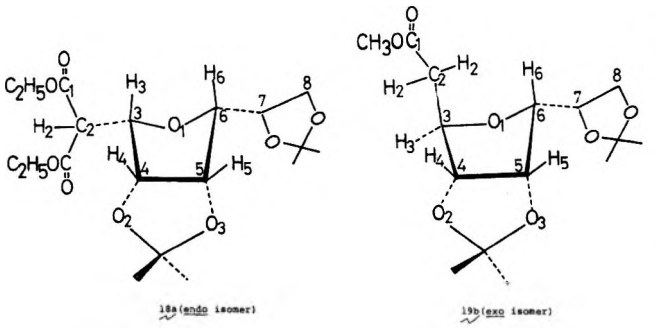

Figure 7.

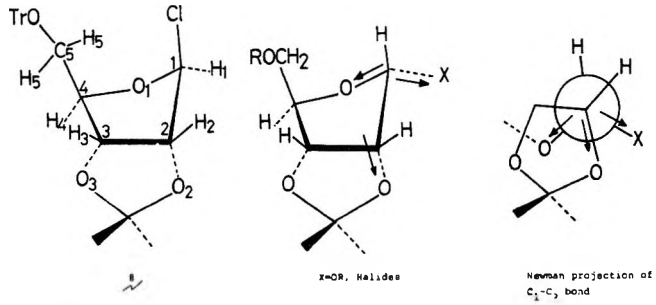

Figure 8.

methylene groups in the exo isomer **15b**. On the other hand, there is only one 1,3-diaxial interaction between the trityloxy methylene group and H_3 in the endo isomer **15a**. The sum of the former interactions apparently exceeds that of the latter one. Thus, the endo isomers are thermodynamically more stable than the exo isomers.

The relative stabilities of D-allofuranosyl derivatives can be rationalized by the same discussions used for D-ribofuranosyl derivatives if the trityloxy methylene group is replaced by the 1,3-dioxolane substituent.

When the coupling constants of the tetrahydrofuran ring protons of α-D-mannofuranosyl *C*-glycosides (exo isomer) and those of α-D-ribofuranosyl *C*-glycosides (endo isomer) are compared, it is easily recognized that the conformation of the tetrahydrofuran ring of the α-D-mannofuranosyl *C*-glycosides (exo isomers) is the same as that of α-D-ribofuranosyl *C*-glycosides (endo isomers) but the mirror image as shown in Figure 7 using compound **19b**. On the other hand, the coupling constants of β-D-mannofuranosyl *C*-glycosides **18a** (endo isomer) are $J_{3,4} = 3.5$, $J_{4,5} = 6$, and $J_{5,6} = 3$ Hz. The $J_{3,4}$ and the $J_{4,5}$ of **18a** are the same as those of α-D-ribofuranosyl *C*-glycoside (endo isomer). The fact that the endo isomer **18a** has very similar $J_{3,4}$ and $J_{5,6}$ indicates that the conformation of the tetrahydrofuran ring of **18a** will be symmetrical. Thus, the conformation of **18a** is the oxygen atom down envelope form (*Eo*) which is very similar to **15a** in Figure 5 but more C_6 up as shown in Figure 7. It is very reasonable that the endo substituent at C_6 of **18a** takes a more quasi-equatorial orientation than the H_6 of **15a** (more C_6 up conformation of **18a** than **15a**).

In the conformation of **18a** in Figure 7, the interactions caused by the two methylene group at C_3 and C_6 are minimized, because they take the quasi-equatorial orientation. The instability factors that should be taken into consideration in this conformation are the interactions caused by the ring protons, because they sit on the same side of the tetrahydrofuran ring. It is apparent that the sum of the interactions of compounds **18a** is smaller than that of compound **19b**. Therefore, the endo isomer is thermodynamically more stable than the exo isomer.

Thus, the order of the relative thermodynamic stability of

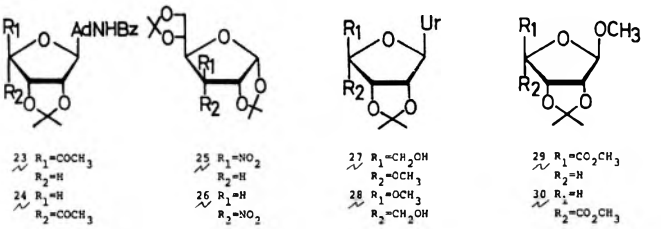

Figure 9.

these *C*-glycosyl compound is **18a** > **19b** or **15a** > **15b**. It is very interesting that the order is completely reverse of that which would be expected based on the generally accepted concept, in spite of the fact that there are two endo substituents in the most stable structure, there is one endo substituent in the next stable structure, and there is no endo substituent in the most unstable structure.

Very recently Wertz and Allinger[20] have proposed a very challenging rationalization on the conformational analysis of organic compounds that *the H/H gauche interactions are not negligible, and in fact may be the most important contributors to the gauche effect*. However, it seems that the gauche effects such as O/H and H/CH_2OR are playing a more important role than H/H gauche interactions in these *C*-glycosyl compounds.

As described in the beginning of this paper, aglycons such as OR and halides exist primarily in the trans C_1, C_2 configuration in these fused five-membered ring systems. In order to clarify the factors that make the exo isomers thermodynamically more stable than the endo isomers in the case of *O*-glycosides and halogeno sugars in this system, the conformational analysis of compound **7** was next undertaken. The coupling constants of the tetrahydrofuran ring protons of **7** are $J_{1,2} = 0$, $J_{2,3} = 5.8$, and $J_{3,4} = 1.8$ Hz. These coupling constants indicate that the conformation of **7** is very similar to that of **15a** but a little C_4 down envelope form. It is very reasonable that compound **7** has more C_4 down conformation than **15a** to decrease the 1,3-interaction between the chlorine atom and the trityloxy methylene group. The difference between halogeno sugars or *O*-glycosides and *C*-glycosides is the presence of a dipole between C_1 and the polar aglycons in the former case. If halides or OR take the endo configuration (quasi-equatorial orientation), the dipole between C_1 and the polar aglycon becomes parallel to other dipoles caused by the oxygen atoms in the molecule as shown in Figure 8. The dipole interactions destabilize the endo configuration. Therefore, the electronegative groups exist mainly in the quasi-axial orientation (trans C_1,C_2 relation) in this system.

Several other examples of isopropylidene sugars that prefer to exist in an endo (cis to the *O*-isopropylidene group) configuration are found in the literature. Moffatt et al.[21] showed that 5′-keto nucleoside **23** rapidly epimerized at $C_{4'}$ giving **24** upon chromatography on silicic acid; Kovar and Baer[22] reported the base-catalyzed epimerization of nitro sugar **25** to the more stable **26**. The acid-catalyzed equilibration of 4′-methoxyuridine (**27**) gave the more stable α-L-lyxo nucleoside (**28**).[23] A recent observation on the base-catalyzed epimerization of methyl (methyl 2,3-*O*-isopropylidene-β-D-ribofuranosyl)uronate (**29**) to the more stable α-L-lyxofuranosyluronate (**30**) was reported.[24] All of these facts can be explained based on the rationalization proposed above.

Experimental Section

Proton nuclear magnetic resonance (^1H NMR) spectra were obtained using a Varian HA-100 spectrometer.

X-Ray Crystallography. Unit cell parameters and intensity data were obtained with a Syntex $P2_1$ diffractometer using monochromatized Mo Kα radiation. Calculations were performed using the

Syntex XTL system, and the solution of the structure was served by the conventional heavy-atom method. The position of the bromine atom of **22a** was determined from a Patterson function, and subsequent Fourier synthesis, based on the phase angles due to the bromine atom, located other atoms. The refinement was concluded by eight cycles of full matrix least squares in which positional parameters of all atoms and anisotropic temperature factors of all atoms other than hydrogens were included. Atomic scattering factors are those of Cromer and Waber,[25] and anisotropic temperature factors fell in normally encountered ranges. For structure of **22a**, the crystals were orthohombic, a = 5.775 (5), b = 11.878 (6), c = 25.007 (6), and were in space group $P2_12_12_1$; Z = 4, $F(000)$ = 808. The calculated density was 1.53 cm^{-1}, and the linear absorption coefficient was 25.7 cm^{-1} for Mo Kα. Of the 1347 reflections in the range $0 < 2\tau < 45$ that were measured using the scan technique, 1074 had an intensity greater than 1.96 times the standard deviation and were recorded as observed. The final R value for the crystal during data collection was suggested by a somewhat larger value of B_{11} for the bromine atom.

The final positional and thermal parameters are in Tables IV and V.

Acknowledgment. We are grateful to Drs. J. J. Fox, Sloan-Kettering Institute for Cancer Research, and J. G. Moffatt, Syntex Research, for useful discussion. The authors wish to express their thanks to Dr. K. Aoki for x-ray study and Mr. J. Uzawa for NMR study.

Registry No.—**12a**, 56703-38-9; **12b**, 56703-37-8; **13a**, 56781-38-5; **13b**, 56781-37-4; **14a**, 56703-39-0; **14b**, 56752-57-9; **15a**, 56779-60-3; **15b**, 56703-40-3; **16a**, 56703-41-4; **16b**, 55036-19-6; **17a**, 56703-43-6; **17b**, 56703-42-5; **18a**, 52921-56-9; **18b**, 52921-55-8; **19a**, 56703-46-9; **19b**, 56703-45-8; **22a**, 56703-44-7; **22b**, 57078-06-5.

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Proton Magnetic Resonance Spectra of Cubane Derivatives. 3. Transmission of Substituent Effects in 4-Substituted 1-Bromohomocubane Derivatives

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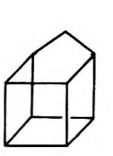
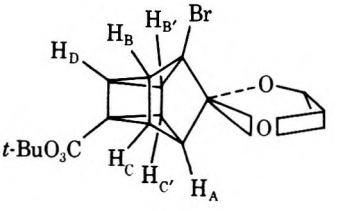
An analysis of the NMR spectra of some homocubane derivatives is reported and shown to be in accord with a previous study of cubane NMR spectra. The results obtained have been interpreted in terms of a through-space mechanism for both cross-ring coupling and the transmission of substituent effects in these systems.

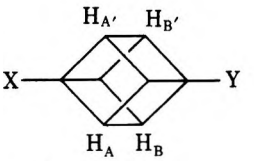
In the first paper[1] of this series we reported our analyses of the NMR spectra of cubane and various mono- and 1,4-disubstituted cubanes, and examined the effects of substituents upon the observed chemical shifts and coupling constants. Such information should assist in the subsequent analysis of the spectra and structures of related cage compounds. Analyses for systems related to cubanes may then be compared with that for cubanes to examine the effects of ring expansion, relative substituent geometries, strain, etc., as subtle differences arising from such effects should be reflected in the observed NMR spectra.[2] In the present paper such a comparison is made for some derivatives of homocubane (I), data from the previous study being used to assist in the detailed analysis of the spectrum of 1-bromohomocuban-9-one-4-carboxylic acid ethylene ketal *tert*-butyl perester (II).



I



II

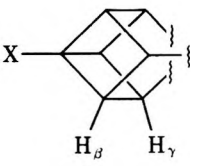


$J_{AB} = J_{ortho}$

$J_{AA'}, J_{BB'} = J_{meta}$

$J_{A'B} = J_{para}$

III



IV

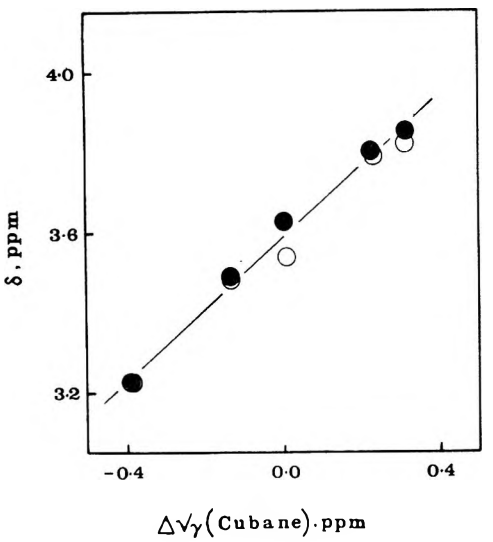


Figure 2. A comparison of substituent effects upon the chemical shifts of the β-hydrogen atoms in cubanes and the corresponding 4-substituted 1-bromohomocuban-9-one ethylene ketals: ●, H_C values; ○, H_D values. Slope = 0.9.

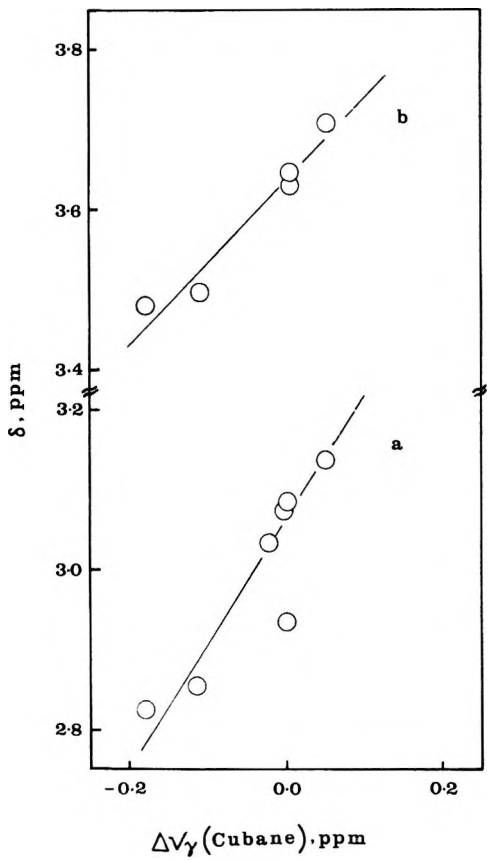


Figure 3. A comparison of substituent effects upon the chemical shifts of the γ-hydrogen atoms in cubanes and the corresponding 4-substituted 1-bromohomocuban-9-one ethylene ketals: a, H_A values; b, H_B values.

The NMR spectra were measured in $CDCl_3$ at 100 MHz on a Varian HA-100 spectrometer as described previously.[1] Some spectra were also measured at 220 MHz by the Canadian 220-MHz NMR Centre in an attempt to obtain sufficient information for the complete analysis of the spectra of the 9-ketals. Reported values are considered accurate to ±1.5 Hz and were reproducible within ±0.5 Hz.

In a 1,4-disubstituted homocuban-9-one (or derivative) there are nine ring proton–proton coupling constants which may be classified as "ortho", "meta", or "para", following Cole's terminology[3] for the cubane system (e.g., III). Using typical coupling constants for the corresponding cubanes as first estimates, the 100-MHz spectra of the 4-CH_3 and 4-CO_3-*t*-Bu derivatives of 1-bromohomocuban-9-one ethylene ketal were analyzed using the LAOCN3 program.[7] The data from these analyses were then iterated to obtain the best fit with the experimental data. The 220-MHz spectrum of the 4-CO_3-*t*-Bu derivative (II) was similarly analyzed and from these two sets of data coupling constants and chemical shifts giving a good fit to both experimental spectra were obtained. This detailed analysis of the 220-MHz spectrum was not repeated for other ketals because of accidental shift equivalences, etc., but the predicted spectra for the compounds of Table II, obtained using the coupling constants for II (Table I), are in good qualitative agreement with their measured spectra.

The $[AB]_2$ spectrum of the ethylene ketal group was also analyzed using initial coupling constant values obtained by Abraham[8] for 2-methyl-1,3-dioxolane. Both solvent effects and the nature of the 4 substituent were found to have an insignificant effect upon these coupling constants. (The calculated and observed spectra of II are compared in Figure 1; see paragraph at end of paper regarding supplementary material.)

Table I. Chemical Shifts (±1 Hz) and Coupling Constants (±0.3 Hz) Obtained from the 220-MHz Spectrum of II (Reference Me_4Si)

	ν_A = 679.6 Hz ν_B = 803.9 Hz ν_C = 849.5 Hz ν_D = 840.4 Hz	
J_{ortho}, Hz	J_{meta}, Hz	J_{para}, Hz
J_{AC} = 5.4	J_{AB} = 0.8	J_{AD} = −0.2
J_{BC} = 7.2	$J_{BB'}$ = 5.9	$J_{BC'}$ = −0.8
J_{BD} = 5.1	$J_{CC'}$ = 5.6	
	J_{CD} = 1.4	

Table II. 220-MHz Chemical Shifts (Hz) of Cage Protons in 1-Br-4-X-Homocuban-9-one Ethylene Ketals (Reference Me_4Si)

Registry no.	X	ν_A	ν_B	ν_C	ν_D
61752-35-0	CO_3-*t*-Bu	679.6 ± 1	803.9 ± 1	849.5 ± 1	840.4 ± 1
37794-26-6	Br	690 ± 1	816 ± 1	838 ± 3	834 ± 3
56289-81-7	H[a]	647 ± 1	799 ± 1	799 ± 3	779 ± 1
41100-11-2	CH_2OH	630 ± 1	770 ± 8	770 ± 8	770 ± 8
60462-12-6	CH_3	622 ± 1	765 ± 1	712 ± 3	712 ± 3
25867-86-1	CO_2H	677 ± 3[b]			
25867-87-2	CO_2Me	669 ± 3[b]			
41100-28-1	CH_2OTs	629 ± 3[b]			
41100-19-0	CH_2Cl	633 ± 3[b]			

[a] ν_X = 742 ± 1 Hz. [b] Calculated from spectra recorded at 100 MHz.

Discussion

Coupling Constants. The coupling constants determined for cubane derivatives were shown to vary slightly with the electronegativity of the substituents and their magnitudes were interpreted by reference to the molecular geometry. Thus, ortho couplings in these compounds are small because of the strained skeleton in which the H–C–C′ bond angles are considerably greater than those in nonfused cyclobutanes.[9] Meta couplings are larger than the cross-ring couplings of nonfused cyclobutanes, in part because of the approximately planar "W" pathways linking these positions in cubanes.[10] Para couplings are unusually large in cubanes because of the ideal geometry for back-lobe overlap.[1] The introduction of an extra carbon atom into the cubane skeleton allows an examination of the above interpretations, i.e., a comparison of through-bond and through-space interactions.

The coupling constants obtained for II are consistent with the cubane data and these values give reasonably good spectral

agreement with computed spectra for the other homocubanes studied. Ortho couplings range from 5.1 Hz (J_{BD}) to 7.2 Hz (J_{BC}) and compare well with the ca. 5.3 Hz value for cubanes. An examination of the x-ray data[11,12] for compounds analogous to II shows that the H_B–C–C′–H_D bond and dihedral angles are very close to those of cubanes and therefore a cubanelike value of J_{BD} is expected. For similar reasons, the value of J_{AC} (5.4 Hz) is expected to be close to the cubane value (5.3 Hz), as observed. The H_B–C–C′ and C–C′–H_C angles are considerably smaller than the corresponding angles in cubane derivatives, however, and this leads to a larger value of J_{AC} in the homocubane derivative (7.2 Hz).

A much greater range of coupling constant values is found for the meta protons, varying from J_{AB} = 0.8 Hz to $J_{BB'}$ = 5.9 Hz (cf. 2.5 Hz for cubanes). Of the six faces of the homocubane cage two are formed by planar four-membered rings as in cubane, two by puckered four-membered rings, and two by five-membered rings. Thus the coupling constant across a planar four-membered ring should be the most similar to that found in the cubanes, as is observed (J_{CD} = 1.4 Hz). The "meta" coupling across the face of a five-membered ring should be the least "cubanelike" and comparable with values for other fused cyclopentanes. The small value obtained here (J_{AB} = 0.8 Hz) is consistent with both the decreased strain in this ring and the fact that there is only one, rather than two, four-bond pathway linking H_A and H_B. The faces of the cage across which the remaining meta couplings occur ($J_{BB'}$ and $J_{CC'}$) are puckered four-membered rings. One result of this is to make the "W" pathway linking the coupled protons more nearly planar. This effect may explain the remarkably large values of $J_{BB'}$ and $J_{CC'}$ (5.9 and 5.6 Hz, respectively) obtained, as such a planar W orientation is especially favorable for four-bond couplings.[13]

Although the observed para coupling constants in II are both small and negative (J_{AD} = −0.2, $J_{BC'} = J_{B'C}$ = −0.8 Hz), the difference between them is significant. We have pointed out previously that para coupling in cubanes may arise through either back-lobe overlap or a through-bond mechanism.[1] In a homocubane (e.g., III), whereas the diagonally opposed C–H_B and C–$H_{C'}$ bonds are perfectly aligned for back-lobe overlap as in cubanes, the C–H_A and C–H_D bonds are not. Our derived value of $J_{BC'}$ has a value very similar to that of cubanes (−0.7 Hz) but that of J_{AD} is much smaller, in support of a through-space mechanism for this coupling. In terms of a through-bond mechanism, one would expect $J_{BC'}$ to be slightly larger than J_{AD} because there are five five-bond pathways between the diagonally opposite H_B and H_C, but only four such pathways linking H_A and H_D. This small difference would seem insufficient to account for the observed fourfold difference between $J_{BC'}$ and J_{AD}.

Chemical Shifts. The transmission mechanism(s) giving rise to observed substituent effects upon chemical shifts are of considerable interest in view of the continuing studies of intramolecular substituent interactions.[14] To examine such effects one may consider the influence of a substituent in cubane, or at the 1 position of a homocubane, upon the protons attached to the carbon atoms β and γ to that bearing the substituent, i.e., H_β and H_γ in IV. If the substituent effects upon these protons are transmitted with equal efficiency in both cage systems, then there should be a linear relationship *of unit slope* between the observed chemical shifts for protons β or γ to the substituent in the homocubane system (i.e., H_C and $H_D \equiv H_\beta$, H_A and $H_B \equiv H_\gamma$) and $\Delta\nu_\beta$ or $\Delta\nu_\gamma$ for the same substituent on cubane. ($\Delta\nu_\beta$ and $\Delta\nu_\gamma$ represent the differences in chemical shifts, for the β and γ protons respectively, between the substituted and unsubstituted cubanes.)

The appropriate chemical shift data are plotted in Figures 2 (for β protons) and 3 (for γ protons) from which it can be seen that the relationships for the β protons are indeed linear, with slopes approximating unity. For the γ protons, linear relationships are also observed, but the slope for the H_A data differs significantly from unity ($\simeq$1.6).

The distances and bond angles between the substituent and H_B, H_C, and H_D are all very similar to those in cubanes and so it is not surprising that the plots shown in Figures 2 and 3(a) for these protons have slopes near unity. The situation for H_A differs in that it lies on the opposite corner of a puckered four-membered ring, relative to the substituent, and this brings it much closer to the substituent than in the corresponding cubane derivative, where it lies on the opposite corner of a planar four-membered ring. The result of this appears to be a more efficient transmission of substituent effects to H_A in homocubanes than in cubanes, as indicated by Figure 3(b) (slope >1). If the substituent effects were transmitted through bonds one would anticipate that they should be the same in both molecules, and thus it appears that at least a large part of the substituent effect on the H_A proton is transmitted through space. This conclusion is also in accord with the evidence that through-space or "field" effects are important in substituent effects upon reactivities.[14]

Acknowledgment. We are grateful to the National Research Council of Canada for financial support and to McGill University for the award of a J. W. McConnell Fellowship (to G.E.L.).

Supplementary Material Available. The calculated and observed NMR spectrum at 100 MHz for II (Figure 1) (1 page). Ordering information is given on any current masthead page.

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Synthesis of Benzannelated Bisdehydro[14]-, -[16]-, -[18]-, and -[20]annulenes[1]

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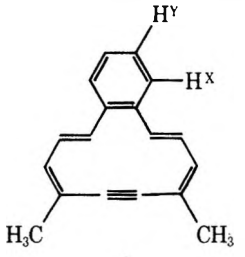
A new synthetic route to benzannelated bisdehydroannulenes is described, which led to the bisdehydrobenz[14]-annulenes **14** and **2**, the bisdehydrobenz[16]annulenes **25** and **26**, and the bisdehydrobenz[18]annulenes **35** and **36**, as well as the bisdehydrobenz[20]annulene **41**. The electronic and ^{1}H NMR spectra of the various benzannelated bisdehydroannulenes are discussed.

Macrocyclic annulenes containing an annelated benzene ring are an interesting class of compound, since the effect of each π system on the other can be studied. In particular, it has been calculated that in such substances the π-bond orders for the benzene rings depend characteristically on the number of π electrons in the annulene rings.[2] Until now, the only known representatives were the dimethylmonodehydrobenz[12]annulene **1** (no particular conformation implied)[3] and



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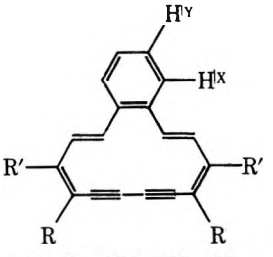
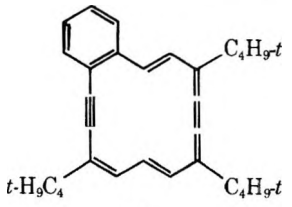


2, R = CH_3; R′ = H
3, R, R′ = $-(CH_2)_4-$



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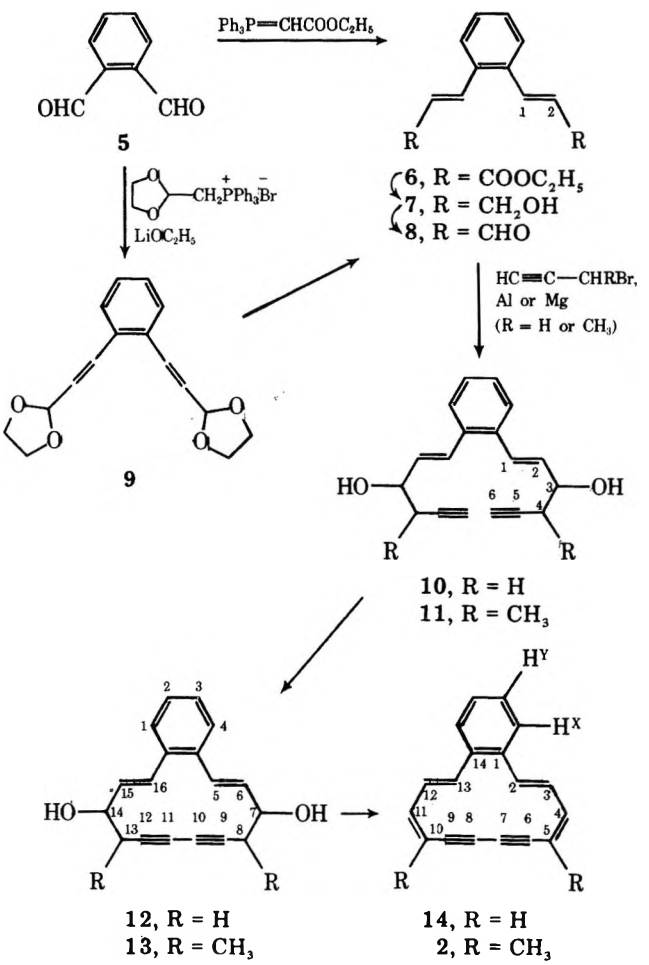
the alkylated bisdehydrobenz[14]annulenes **2**,[4] **3**,[4] and **4**.[5,6] Unfortunately, the dehydrobenzannulenes **1**, **2**, and **3** synthesized in our laboratories were obtained only in poor yield, and the methods used necessitated the presence of alkyl groups in the final products. We have now developed a greatly improved synthesis of bisdehydrobenzannulenes, which often proceeds in satisfactory yield, and appears to be of general applicability. In this paper we describe the use of this new synthesis for the preparation of the unsubstituted bisdehydrobenz[14]annulene **14**, -[16]annulene **25**, -[18]annulene **35**, and -[20]annulene **41**, as well as the dimethyl derivatives **2**, **26**, and **36** in the 14-, 16-, and 18-membered ring series, respectively.[7] The dimethyl derivatives were prepared in addition to the unsubstituted ones, since they were required as models for comparison with annulenoannulenes containing the same alkylation pattern.[8]

The synthesis of the bisdehydrobenz[14]annulene **14** (Scheme I) illustrates the method. Wittig reaction of *o*-phthalaldehyde (**5**) with 2 molar equiv of carbethoxymethylenetriphenylphosphorane[9] in boiling methylene chloride yielded 79% of the di-trans ester **6**. This substance was then converted to the dialdehyde **8** in 51% overall yield by reduction to the diol **7** with diisobutylaluminum hydride, followed by oxidation with manganese dioxide.[10] Alternatively, the transformation of **5** to **8** could be effected in ~50% yield by Wittig reaction of **5** with 1,3-dioxolan-2-ylmethyltriphenyl-

Scheme I



phosphonium bromide[11] and lithium ethoxide to give the bisacetal **9** (stereoisomeric mixture), followed by hydrolysis with hydrochloric acid.

Grignard reaction of the dialdehyde **8** with an excess of the aluminum derivative of propargyl bromide[12] led to a stereoisomeric mixture of the diols **10** in 92% yield. This mixture in aqueous ethanol, benzene, and hydrochloric acid was subjected to oxidative coupling with oxygen in the presence of cuprous chloride and ammonium chloride at 60 °C ("Glaser conditions"). The resulting crude stereoisomeric macrocyclic diols **12** (68% yield) were then treated with 2 molar equiv of methanesulfonyl chloride and triethylamine[13] to give the corresponding dimethanesulfonates, which were subjected to elimination with 2 molar equiv of 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN). This procedure furnished 65% of the desired bisdehydrobenz[14]annulene **14** (40% overall yield from the dialdehyde **8**) as relatively stable, golden yellow needles. Alternatively, the bisdehydrobenz[14]annulene **14** could be obtained directly from the diols **12** in 25% yield by dehydration

with phosphorus oxychloride and pyridine in dimethoxyethane.

The dimethylbisdehydrobenz[14]annulene **2** was obtained analogously (Scheme I). Grignard reaction of the dialdehyde **8** with an excess of the magnesium derivative of 3-bromo-1-butyne[12,14] gave a mixture of the stereoisomeric diols **11**. In this case, the oxidative coupling was carried out with anhydrous cupric acetate[15] in pyridine at 50 °C.[16] The resulting diols **13** were then converted to the corresponding dimethanesulfonates, which were subjected to elimination with DBN. The dimethylbisdehydrobenz[14]annulene **2**, obtained in 37% yield from the dialdehyde **8**, proved to be identical with that obtained previously.[4] The presently described synthesis of **2** is greatly superior to the previous one,[4] since the double bonds adjacent to the benzene ring are introduced stereospecifically in the required trans configuration, and the oxidative coupling of terminal diacetylenes of type **10** and **11** containing hydroxyl groups usually proceeds in much better yield than when the coupling is carried out with hydrocarbons using normal dilutions.[17]

The intermediate required for the synthesis of the bisdehydrobenz[16]annulenes **25** and **26** (Scheme II) was the dialdehyde **18**, a vinylog of the above described dialdehyde **8**. Substance **18** could be obtained by two routes. The preferred one used the diol **7** as starting material, which on oxidation with a limited amount of manganese dioxide gave the monoaldehyde **15** in 56% yield. Reaction of **15** with the salt obtained from triethyl phosphonoacetate and sodium hydride[19] led to the ester **16**, which on reduction with diisobutylaluminum hydride to **17** and subsequent oxidation with manganese dioxide gave 51% (based on **15**) of the dialdehyde **18**.

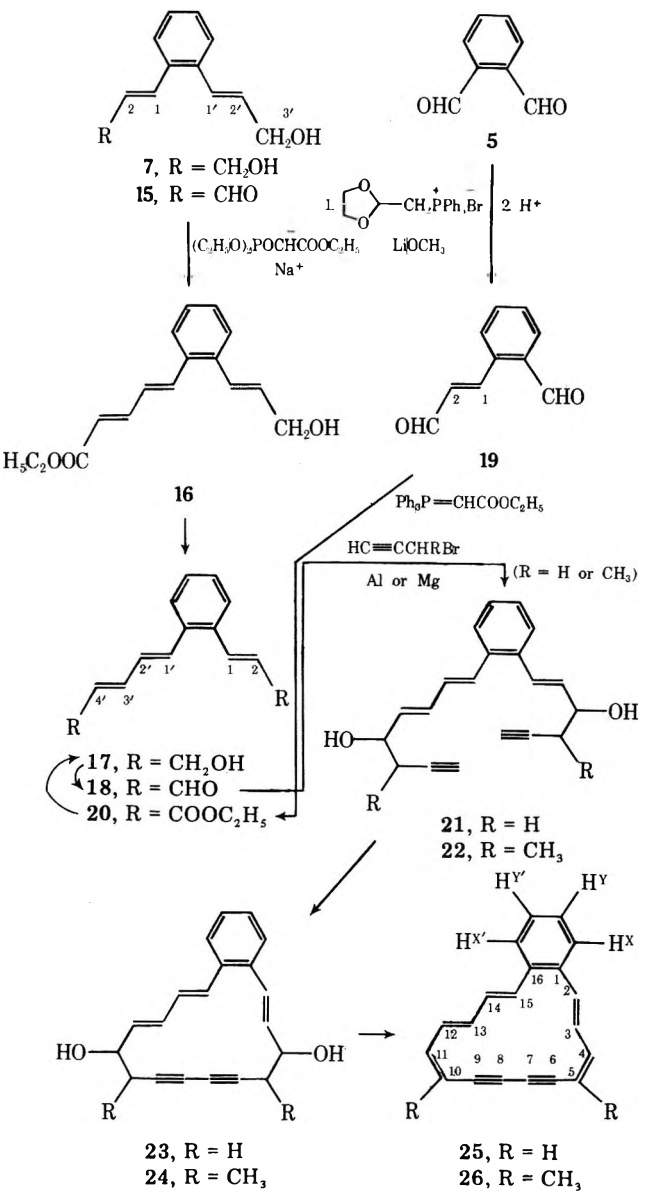
The second route to **18** involved Wittig reaction of o-phthalaldehyde (**5**) with 1 molar equiv of 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide[11] and lithium methoxide, followed by hydrolysis with hydrochloric acid, to give the monovinylog **19** in 18% yield. Treatment of **19** with 2 molar equiv of carbethoxymethylenetriphenylphosphorane[9] then led to 80% of the diester **20**, which could be converted to the dialdehyde **18** via the diol **17** in 62% yield by reduction with diisobutylaluminum hydride and subsequent oxidation with manganese dioxide.

The conversion of the dialdehyde **18** to the bisdehydrobenz[16]annulene **25** (by the sequence **18** → **21** → **23** → **25**; overall yield 53%) and to the dimethylbisdehydrobenz[16]annulene **26** (by the sequence **18** → **22** → **24** → **26**; overall yield 18%) was carried out essentially as described for the corresponding bisdehydrobenz[14]annulenes **14** and **2**, except that both **21** and **22** were oxidatively coupled by means of cupric acetate monohydrate in dimethylformamide at 50–60 °C. The annulenes **25** and **26** formed red needles, mp 98–99 and 133–134 °C, respectively.

Several methods were investigated for the synthesis of the dialdehyde **30**, the intermediate required for the preparation of the bisdehydrobenz[18]annulenes **35** and **36** (Scheme III). The most convenient one involved the Wittig reaction of o-phthalaldehyde (**5**) with 2 molar equiv of the ylide **27**.[20] The resulting diester **28**, obtained as a stereoisomeric mixture in 82% yield, was then reduced with diisobutylaluminum hydride to the diols **29**. Oxidation with manganese dioxide and subsequent isomerization with iodine led to the all-trans dialdehyde **30** in 34% yield (based on **28**). The subsequent steps paralleled the ones used for the syntheses of the benzannelated bisdehydro[14]- and bisdehydro[16]annulenes. The bisdehydrobenz[18]annulene **35** (dark red needles) and the dimethylbisdehydrobenz[18]annulene **36** (orange needles, mp 214–216 °C) were obtained thereby in 21 and 11% yield, respectively, based on **30**.

The dialdehyde **39**, required for the synthesis of the bis-

Scheme II

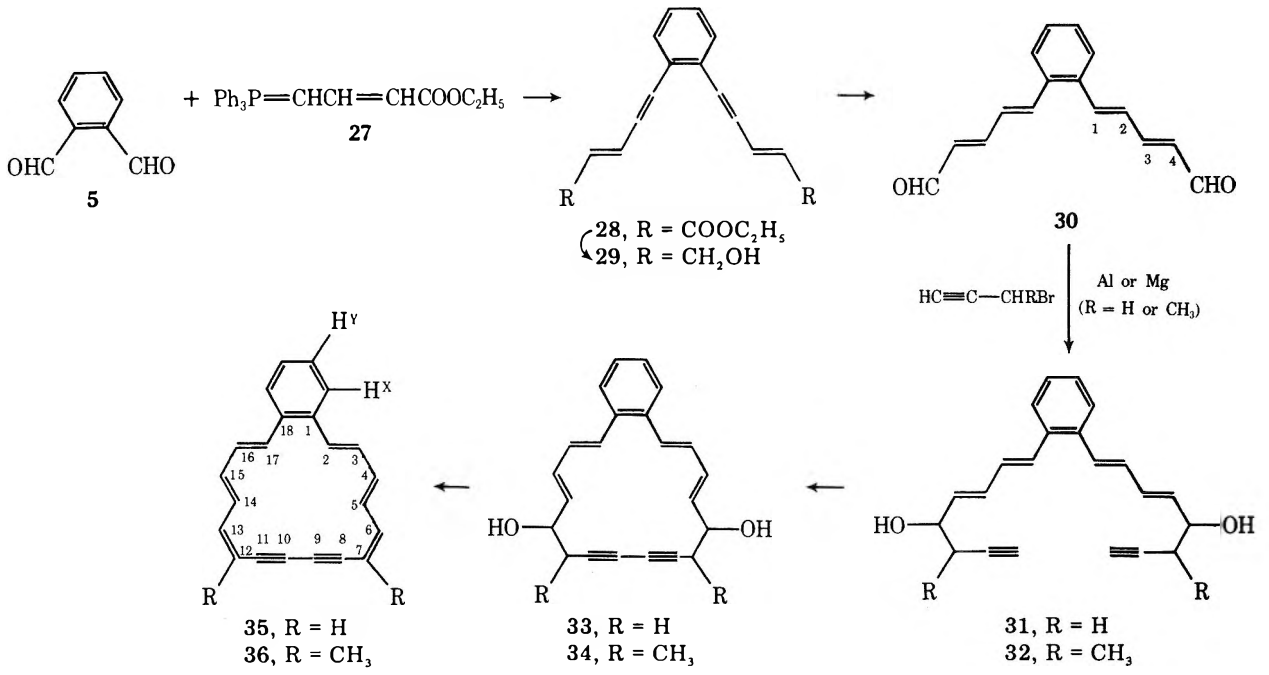


dehydrobenz[20]annulene **41** (Scheme IV), was prepared in 64% yield by the Wittig reaction of the dialdehyde **18** with 2 molar equiv of carbethoxymethylenetriphenylphosphorane[9] followed by reduction of the resulting diester **37** with diisobutylaluminum hydride and oxidation of the diol **38** with manganese dioxide. The usual reaction sequence (Scheme IV) then gave the bisdehydrobenz[20]annulene **41** in 20% overell yield (based on **39**) as purple-brown crystals.

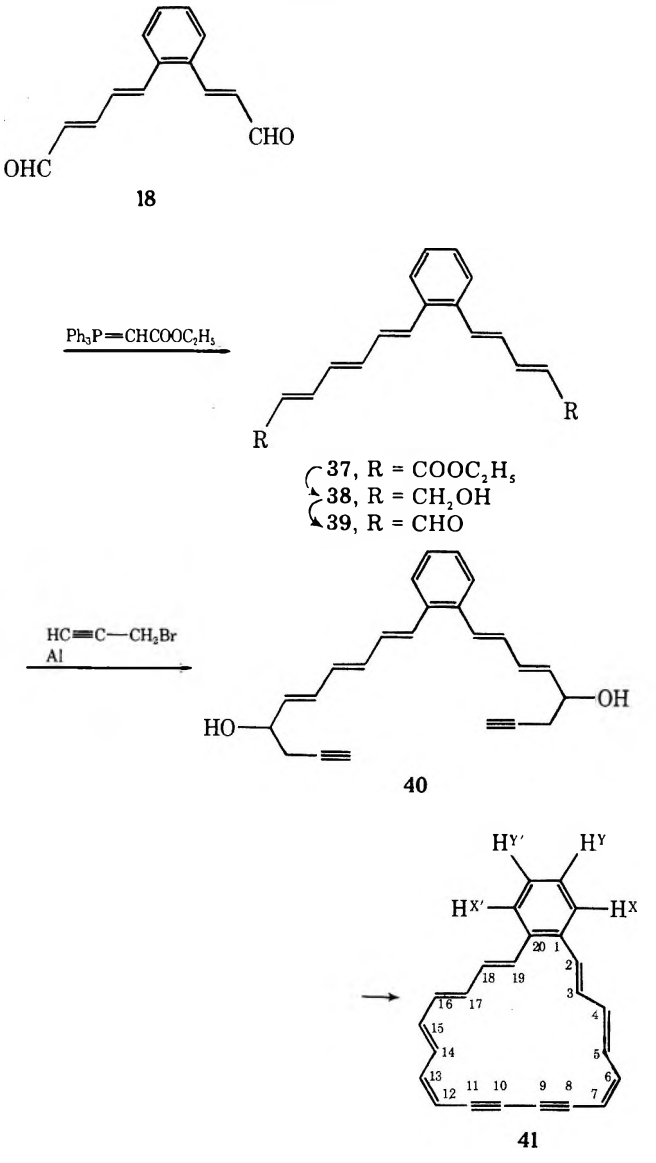
The electronic spectra of the various bisdehydrobenzannulenes were complex (see Experimental Section). The main maxima are given in Table I, as well as those of the nonannelated and unsubstituted bis- or trisdehydroannulenes.[21] It is evident that in the benzannelated compounds the same alternation in the wavelengths of the main maxima of $(4n + 2)$ and $4n$ π systems occurs, as has already been observed for the monocyclic annulenes[22a] and dehydroannulenes.[22b] For each ring size, fusion of the benzene ring results in an appreciable bathochromic shift (4–16 nm), but the introduction of the methyl groups into the benzannulenes causes only a very small bathochromic shift (1–3 nm).[23]

The ^{1}H NMR spectra of the various bisdehydrobenz[14]-, -[16]-, and -[18]annulenes, given in the Experimental Section, confirm the assigned structures and indicated conformations. We have already discussed[4,8] that the spectra show the macrocyclic rings in the dimethylbisdehydrobenz[14]annulene **2**

Scheme III



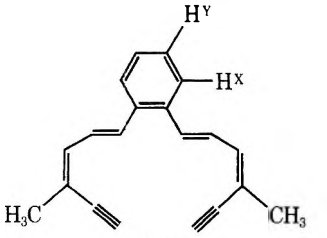
Scheme IV



and -[18]annulene **36** to be diatropic, and in the dimethylbisdehydrobenz[16]annulene **26** to be paratropic, although the ring currents have been reduced by fusion of the benzene rings.[24] Examination of the ^{1}H NMR spectra of the corresponding nonalkylated bisdehydrobenzannulenes **14, 35,** and **25** indicates that the two methyl groups, as expected, cause little effect, although generally the macrocyclic ring currents of the nonalkylated compounds appear to be slightly greater than those of the dimethyl series.

The ^{1}H NMR spectrum of the bisdehydrobenz[20]annulene **41** exhibited a 5 H low-field and a 9 H high-field band due to the olefinic protons, showing the 20-membered ring to be paratropic (although the magnitude of the ring current was again less than in a nonbenzannelated bisdehydro[20]annulene[22c]). This observation, together with the method of synthesis, also indicates **41** to possess the indicated configuration, although a definite conformation could not be assigned in this case.

It is also of interest to examine the effect on the ^{1}H NMR resonances of the benzene ring caused by annelation of the macrocyclic π systems. In the model system **42**,[4] the H^X pro-



42

tons resonate at τ 2.47 and the H^Y protons at τ 2.78 (in $CDCl_3$), the assumption being made that H^X is more affected than H^Y by the unsaturated substituents. Compared with this model, it is clear from Table II that fusion of 14- and 18-membered rings ($4n + 2$ series) causes a downfield shift of the benzenoid proton resonances, this effect being greater for H^X than for H^Y. Conversely, fusion of 12-, 16-, and 20-membered rings ($4n$ series) causes an upfield shift of the benzene resonances; undoubtedly the effect is again greater for H^X (and H$^{X'}$) than H^Y (and H$^{Y'}$), resulting in these resonances appearing as relatively narrow bands. These observations must arise from the

Table I. Main Electronic Absorption Maxima of the Bisdehydrobenzannulenes 2, 14, 25, 26, 35, 36, and 41, and of Nonannelated Analogues, in Ether or 2,2,4-Trimethylpentane (nm; ϵ Values in Parentheses)

Ring size	Bisdehydro-benzannulene	Dimethylbisdehydro-benzannulene	Bisdehydro- or trisdehydro-annulene[a]	
[14]	**14**, 317 (49 100)	**2**, 318 (54 000)	1,7-	304 (83 000)
			1,8-	310 (210 000)
[16]	**25**, 297 (61 400)	**26**, 298 (81 500)	1,3-	281 (55 000)
			1,9-	283 (54 000)
[18]	**35**, 339 (68 700)	**36**, 342 (64 600)	1,7,13-I-	335 (190 000)
			1,7,13-II-	331 (166 000)
[20]	**41**, 324 (95 300)		1,11-	319 (109 000)

[a] See ref 22b.

Table II. Benzenoid ^{1}H NMR Chemical Shifts of Benzannelated Dehydroannulenes at 100 MHz in $CDCl_3$ (τ Values; Internal Standard, Me_4Si)

Registry no.	Dehydrobenzannulene	H^X ($H^{X'}$)	H^Y ($H^{Y'}$)
52421-94-0	Model system **42**[a]	2.47	2.78
59035-73-3	Dimethylmonodehydro[12]-, **1**[b]	2.92	2.92
61650-35-9	Bisdehydro[14]-, **14**[c]	1.69	2.50
61650-36-0	Dimethylbisdehydro[14]-, **2**[a]	1.75	2.49
61650-37-1	Bisdehydro[16]-, **25**	2.8–3.3	
61650-38-2	Dimethylbisdehydro[16]-, **26**	2.9–3.2	
61675-26-1	Bisdehydro[18]-, **35**[c]	1.90	2.49
61650-39-3	Dimethylbisdehydro[18]-, **36**	1.94	2.58
61650-40-6	Bisdehydro[20]-, **41**	2.8–3.2	

[a] Reference 4. [b] Reference 3. [c] The specific assignments of the H^X and H^Y resonances in these compounds were confirmed by long-range coupling observed between H^X and the α protons in the annulene ring (H. Günther, private communication).

predominance of the deshielding of the dehydro[$4n + 2$]-annulenes and shielding of the dehydro[$4n$]annulenes over the ring current of the fused benzene ring.

It was clearly of interest to investigate the benzene π-bond order of the dehydrobenzannulenes described in this paper, in view of the work of Günther et al.,[2] and several of these substances were sent to Professor Günther (University of Cologne) for this purpose. Unfortunately, in the demethyl series, the 16- and 20-membered ring compounds **25** and **41** decomposed during transit, whereas the 14- and 18-membered ring compounds **14** and **35** were essentially unchanged. This shows that "aromatic" macrocyclic ($4n + 2$) systems are more stable than "antiaromatic" $4n$ systems![25] The results obtained with **14** and **35**, as well as with the dimethylbisdehydrobenz-[16]annulene **26** (which proved to be considerably more stable than the demethyl analogue **25**), will be reported subsequently.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were measured on a Unicam SP 200 spectrophotometer or on a Perkin-Elmer 177 grating spectrophotometer (s = strong, m = medium, w = weak); only significant maxima are reported. Electronic spectra were determined on a Unicam SP 800 or a Unicam SP 1800 spectrophotometer (sh = shoulder). ^{1}H NMR spectrum were recorded as $CDCl_3$ solutions on a Varian T-60 (60 MHz), a Varian HA-100 (100 MHz), or a Perkin-Elmer R34 (220 MHz) spectrometer, tetramethylsilane being used as internal standard. Assignments were clarified by the use of decoupling experiments where necessary. Mass spectra were determined on an AEI MS-12 or (for accurate mass measurements) on an AEI MS-902 spectrometer, both operating at 70 eV. Alumina for column chromatography refers to Woelm activity III and silica to Woelm activity II. Compounds were preadsorbed from ether or dichloromethane solution onto the adsorbent before column chromatography on the same adsorbent. Benzene, dimethylformamide (DMF), and 1,5-diazabicyclo[5.4.0]non-5-ene (DBN) were stored over 4 Å molecular sieves for a prolonged period before use. Petrol (light petroleum, bp 40–60 °C) was distilled from P_4O_{10} before use. Tetrahydrofuran (THF) was refluxed over $LiAlH_4$ and distilled under argon before use. 1,2-Dimethoxyethane (DME) was distilled from $LiAlH_4$ before use. Reactions were carried out under prepurified nitrogen and organic extracts were dried over magnesium sulfate before solvent removal.

1,2-Bis(2-ethoxycarbonylethenyl)benzene (6).[10] A solution of *o*-phthalaldehyde (**5**, 24.8 g, 0.185 mol) in dichloromethane (200 mL) was added dropwise over 1 h to a stirred solution of carbethoxymethylenetriphenylphosphorane[9] (129 g, 0.37 mol) in dichloromethane (1 L). The solution was then boiled under reflux for 19 h, acetone (25 mL) was added, and boiling was continued for a further 1 h. The solvents were removed under reduced pressure and the residue was extracted with ether (7 × 150 mL). Evaporation of the ether, removal of triphenylphosphine oxide by filtration as it precipitated, and crystallization from methanol yielded the trans,trans diester **6** (40.1 g, 79%) as prisms: mp 78–79 °C (lit.[26] mp 81 °C); IR ($CHCl_3$) 1710 s (COOEt), 1640 s (C=C), 975 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz) τ 1.93 (d, $J_{1,2}$ = 16 Hz, H-1), 2.3–2.7 (m, benzenoid H), 3.63 (d, $J_{2,1}$ = 16 Hz, H-2), 5.68 (q, $CO_2CH_2CH_3$), 8.64 (t, $CO_2CH_2CH_3$).

1,2-Bis(3-hydroxy-1-propenyl)benzene (7).[10] A solution of diisobutylaluminum hydride (50 mL) in dry benzene (100 mL) was added dropwise over 1 h to a stirred solution of the diester **6** (17.0 g) in benzene (600 mL) at ambient temperature (water bath cooling). The mixture was allowed to stand overnight, and methanol (300 mL) was then added. The mixture was filtered, the solid was washed well with methanol, and the solvents were evaporated. Crystallization from methanol yielded the diol **7** (7.67 g, 65%) as prisms: mp 91–91.5 °C; IR ($CHCl_3$) 3330 s (broad, OH), 965 cm^{-1} s (trans HC=CH); ^{1}H NMR (60 MHz) τ 2.4–3.0 (m, benzenoid H), 3.05 (d, $J_{1,2}$ = 16 Hz, H-1), 3.80 (dt, $J_{2,1}$ = 16, J_{2,CH_2} = 6 Hz, H-2), 5.65 [d(b), $J_{CH_2,2}$ = 6 Hz, CH_2], 8.10 [s(b), OH].

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.35.

1,2-Bis(2-formylethenyl)benzene (8). A. From the Diol 7.[10] The diol **7** (7.5 g) in dichloromethane (1.1 L) was stirred with activated manganese dioxide[27] (75 g) at ambient temperature for 23 h. The mixture was filtered through Celite, and the solid was washed well with dichloromethane. Evaporation of the solvent and crystallization from ethyl acetate gave the dialdehyde **8** (5.84 g, 79%): mp 115–116 °C; IR ($CHCl_3$) 1680 s (C=O), 970 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz) τ 0.25 (d, $J_{CHO,2}$ = 8 Hz, CHO), 2.10 (d, $J_{1,2}$ = 16 Hz, H-1), 2.15–2.7 (benzenoid H), 3.37 (dd, $J_{2,1}$ = 16, $J_{2,CHO}$ = 8 Hz, H-2).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.03; H, 5.47.

B. From *o*-Phthalaldehyde (5) via the Bisacetal 9. A solution of lithium ethoxide, prepared by dissolving lithium (210 mg, 30 mg-atoms) in dry ethanol (50 mL), was added dropwise during 4 h to a stirred solution of 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide[11] (12.9 g, 30 mmol) and o-phthalaldehyde (**5**, 1.34 g, 10 mmol) in dry DMF (100 mL) at 80–90 °C (bath) under a reflux condenser. After a further 1 h, the reaction mixture was cooled and poured into brine (600 mL). The resultant mixture was extracted with ether (3 × 200 mL), and the combined extracts were washed with brine. Drying and evaporation led to the crude bisacetal **9**, the complex ^{1}H NMR spectrum of which indicated it to be a stereoisomeric mixture. The crude material was hydrolyzed by solution in tetrahydrofuran (50 mL) and addition of 10% hydrochloric acid (50 mL). After being allowed to stand for 3 h at ambient temperature, the solution was extracted with chloroform, and the extracts were washed with sodium bicarbonate solution and water, dried, and evaporated. The residue was chromatographed on a column of silica (75 g) with 30% ethyl acetate–petrol as eluent. Crystallization from ethyl acetate gave the dialdehyde **8** (0.95 g, 51% based on **5**), identical with that prepared by method A.

1,2-Bis(3-hydroxy-1-hexen-5-ynyl)benzene (10). A solution of propargyl bromide (2.04 g, 17 mmol) in dry ether (15 mL) was added dropwise over 15 min to a stirred mixture of small pieces of aluminum foil (0.31 g, 12 mg-atoms), mercuric chloride (70 mg), and dry ether (5 mL) under reflux. The mixture was boiled under reflux for 5 h, cooled to −30 °C, and stirred rapidly while a solution of the dialdehyde **8** (0.85 g, 4.5 mmol) in DME (25 mL) was added over 5 min. The mixture was allowed to warm to 0 °C over 15 min, ice and water were added, and the aqueous layer was extracted with ether. The residue after solvent removal, dissolved in the minimum of chloroform, was chromatographed on a column of silicic acid (3 × 3 cm). Elution with 2% ethanol–chloroform yielded the diol **10** (stereoisomeric mixture, 1.10 g, 92%) as a colorless oil: mass spectrum *m/e* 266 (M^+); IR (film) 3375 m (OH), 3300 m (C≡CH), 2130 w (C≡C), 975 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz) τ 2.78 (m, benzenoid H), 3.05 (d, $J_{1,2}$ = 16 Hz, H-1), 3.85 (dd, $J_{2,1}$ = 16, $J_{2,3}$ = 6 Hz, H-2), 5.56 (m, H-3), 7.02 [s(b), OH], 7.48 (dd, $J_{4,3}$ = 6. $J_{4,6}$ = 2 Hz, H-4), 7.90 (t, $J_{6,4}$ = 2 Hz, H-6).

9,10,11,12-Tetradehydro-7,8,13,14-tetrahydrobenzocyclotetradecene-7,14-diol (12). A solution of the diol **10** (4.0 g, 15 mmol) in ethanol (30 mL) was added to a stirred mixture of cuprous chloride (65 g), ammonium chloride (110 g), water (400 mL), and concentrated hydrochloric acid (6 mL) at 60 °C. After 5 min, benzene (240 mL) and ethanol (110 mL) were added, and the mixture was stirred for 2 h while a vigorous stream of oxygen was bubbled into the mixture. The volume was maintained by the periodic addition of benzene–ethanol (5:1). The mixture was then cooled to ambient temperature and sufficient 4 N hydrochloric acid was added to effect dissolution of the salts. The aqueous layer was extracted with ether (3 × 250 mL), and the combined organic phases were dried and evaporated. Trituration of the residue with chloroform afforded the diol **12** (stereoisomeric mixture, 2.72 g, 68%) as a nearly colorless solid: mp >130 °C dec; IR (Nujol) 3300 s (OH), 2275 w (C≡C), 970 s and 960 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz) τ 2.4–3.2 (m, benzenoid H, H-5, H-16), 3.7–4.4 (m, H-6, H-15), 5.2–5.7 (m, H-7, H-14), 7.2–7.7 (m, H-8, H-13). The diol **12** was used in subsequent reactions without further purification.

6,8-Bisdehydrobenz[14]annulene (9,10,11,12-Tetradehydrobenzocyclotetradecene, 14). A. Methanesulfonate Method. A solution of triethylamine (0.67 g, 6.7 mmol) in DME (1.5 mL) was added dropwise over 5 min to a stirred, ice-cooled solution of the diol **12** (0.80 g, 3.0 mmol) and methanesulfonyl chloride (0.73 g, 6.4 mmol) in DME (18 mL). After 20 min at 0 °C, the precipitated salts were removed by filtration and a solution of DBN (0.93 g, 7.5 mmol) in DME (1.5 mL) was added dropwise over 5 min to the ice-cooled stirred filtrate. After a further 5 min, the ice bath was removed and the mixture stirred for 45 min at ambient temperature. The reaction mixture was then poured onto water and extracted with benzene. The residue, after solvent removal, was chromatographed on a column of alumina (5 × 3 cm) with benzene as eluent. Crystallization from hexane led to the benz[14]annulene **14** (0.45 g, 65%) as golden yellow needles: mp >165 °C dec; MS *m/e* 228 (M^+); UV (Et_2O) λ_{max} 262 nm (ϵ 8500), 276 sh (11 000), 317 (49 100), 380 (4000), 398 (3950), 416 sh (2600); IR ($CHCl_3$) 2180 w (C≡C), 985 cm^{-1} m (trans HC=CH); ^{1}H NMR (100 MHz) τ 1.69 (m, H^X), 2.40 (dd, $J_{3,2}$ = $J_{12,13}$ = 16, $J_{3,4}$ = $J_{12,11}$ = 7 Hz, H-3, H-12), 2.50 (m, H^Y), 2.71 (dd, $J_{4,5}$ = $J_{11,10}$ = 11, $J_{4,3}$ = $J_{11,12}$ = 7 Hz, H-4, H-11), 3.58 (d, $J_{5,4}$ = $J_{10,11}$ = 11 Hz, H-5, H-10), 5.44 (d, $J_{2,3}$ = $J_{13,12}$ = 16 Hz, H-2, H-13).

Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.59; H, 5.30.

B. Phosphorus Oxychloride Method. A stirred solution of the diol **12** (0.16 g, 0.6 mmol) and pyridine (0.25 g, 3.2 mmol) in DME (6 mL) was cooled to −30 °C and phosphorus oxychloride (30 drops) was added. The cooling bath was removed after 15 min, and the mixture was stirred at ambient temperature for 19 h. It was then poured onto water and extracted with ether, and the extracts were washed with water. The residue after solvent removal was chromatographed on a column of alumina (3 × 2 cm) with pentane as eluent. Early fractions afforded, after crystallization from hexane, the benz[14]annulene **14** (34 mg, 25%) as golden yellow needles, identical with that prepared by method A.

5,10-Dimethyl-6,8-bisdehydrobenz[14]annulene (8,13-Dimethyl-9,10,11,12-tetradehydrobenzocyclotetradecene, 2). A small portion of a solution of 3-bromo-1-butyne[14] (1.2 g, 9.1 mmol) in dry ether (5 mL) was added to a stirred mixture of magnesium (0.21 g, 8.6 mg-atoms) and mercuric chloride (10 mg) in dry ether (20 mL). When the mixture had become cloudy (~5 min), it was cooled in an ice bath, and the remainder of the bromide solution was added over 2 min. After 2 h at 0 °C, the mixture was cooled to −30 °C, and a solution of the dialdehyde **8** (0.20 g, 1.1 mmol) in THF (10 mL) was added in a thin stream. The resultant mixture was allowed to warm to 0 °C over 15 min, and saturated aqueous ammonium chloride was then added. Extraction with ether, followed by solvent removal, gave the crude diol **11** (stereoisomeric mixture) as an oil (0.38 g).

A solution of crude **11** (0.38 g) in pyridine (20 mL) was added dropwise over 2 h to a stirred solution of anhydrous cupric acetate[15] (4.0 g) in pyridine (100 mL) and dry ether (30 mL) at 50 °C. After a further 1 h at 50 °C, the solution was cooled and the solvents were evaporated. Water was added to the residue, the mixture was extracted with ether, and the organic extract was washed with water. Solvent removal yielded the crude diol **13** (stereoisomeric mixture) as a light brown froth (0.33 g).

A solution of triethylamine (0.22 g, 2.2 mmol) in THF (3 mL) was added over 2 min to a stirred, ice-cooled solution of the crude diol **13** (0.33 g) and methanesulfonyl chloride (0.25 g, 2.1 mmol) in THF (15 mL). After 1.5 h, the salts were separated by filtration, and a solution of DBN (1.3 g, 10.5 mmol) in THF (8 mL) was added dropwise over 10 min to the stirred filtrate with ice cooling. The ice bath was then removed, and the mixture was stirred at ambient temperature for 3 h. The mixture was then poured onto water and extracted with ether, and the extract was washed with water. The residue, after solvent removal, was chromatographed on a column of alumina (6 × 4 cm) with 10% ether–petrol as eluent. Crystallization from dichloromethane–petrol gave the benz[14]annulene **2** (102 mg, 37% based on **8**) as orange needles, mp 176–177 °C (lit.[4] mp 174–175 °C). The electronic and ^{1}H NMR spectra were identical with those reported previously.[4]

Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.49; H, 6.34.

1-(2-Formylethenyl)-2-(3′-hydroxy-1′-propenyl)benzene (15). A solution of the diol **7** (4.3 g, 23 mmol) in dichloromethane (100 mL) was stirred with activated manganese dioxide[27] (16 g) for 15 h. A further quantity (10 g) of manganese dioxide was added, and the mixture was then stirred and heated under reflux for 3 h. The solid was separated by filtration and washed well with dichloromethane. The combined filtrates were dried ($MgSO_4$), concentrated to ~10 mL, and applied to a column of silica gel (10 × 4 cm). Elution with dichloromethane afforded the monoaldehyde **15** (2.35 g, 56%) as a pale yellow gum, homogeneous by TLC examination: MS *m/e* 188 (M^+), 170 ($M^+ - H_2O$), 159 (M^+ − CHO), 158 ($M^+ - CH_2O$), 157 (M^+ − CH_2OH); IR (film) 3410 m (OH), 1672 (C=O), 968 cm^{-1} m (trans HC=CH); ^{1}H NMR (100 MHz) τ 0.34 (d, $J_{CHO,2}$ = 7 Hz, CHO), 2.16 (d, $J_{1,2}$ = 16 Hz, H-1), 2.38–2.80 (m, benzenoid H), 3.03 (dt, $J_{1',2'}$ = 16, $J_{1',3'}$ = 2 Hz, H-1′), 3.38 (dd, $J_{2,1}$ = 16, $J_{2,CHO}$ = 7 Hz, H-2), 3.76 (dd, $J_{2',1'}$ = 16, $J_{2',3'}$ = 6 Hz, H-2′), 5.61 (dd, $J_{3',2'}$ = 6, $J_{3',1'}$ = 2 Hz, H-3′), 7.22 [s(b), OH]. The amount of manganese dioxide needed depends on its activity, and the reaction can be conveniently followed by TLC examination.

1-(2-Formylethenyl)-2-(4′-formyl-1′,3′-butadienyl)benzene (18) from 15. A stirred mixture of the salt obtained from triethyl phosphonoacetate (4.5 g, 20 mmol) and sodium hydride (0.79 g of a 57% mineral oil dispersion rendered oil free by washing with pentane; 19 mmol) in dry benzene (50 mL) was treated dropwise over 15 min with a solution of the monoaldehyde **15** (2.3 g, 12 mmol) in dry benzene (10 mL) at ambient temperature. After a further 30 min, the mixture was poured onto water and extracted with ether, and the extracts were washed with water. Solvent removal resulted in the crude ester **16** (3.64 g) as a viscous, pale yellow gum.

A solution of diisobutylaluminum hydride (4.4 g, 31 mmol) in dry benzene (22 mL) was added dropwise over 20 min to an ice-cooled stirred solution of the crude ester **16** (3.64 g) in dry benzene (50 mL). The ice bath was then removed and the solution was stirred at ambient temperature for 30 min before being recooled in an ice bath. Methanol (5 mL) was added cautiously and the resultant mixture was poured onto ice-cold 2 N hydrochloric acid (150 mL) and extracted with ether. The extracts were washed successively with 2 N hydrochloric acid, saturated sodium bicarbonate solution, and water. Solvent removal gave the crude diol **17** (2.46 g) as a yellow gum.

A solution of the crude diol **17** (2.46 g) in dichloromethane (80 mL) was stirred with activated manganese dioxide[27] (29 g) for 4 h. The solid was separated by filtration and washed well with dichloromethane. Evaporation of the combined filtrates afforded the dialdehyde **18** as a yellow solid (1.33 g, 51% based on **15**), homogeneous by TLC examination. Crystallization from 95% ethanol gave yellow prisms: mp 124–126 °C; MS *m/e* 212 (M^+); UV (EtOH) λ_{max} 288 nm (ϵ 37 900), 333 (38 600); IR (KBr) 1667 s (C=O), 983 m and 972 cm^{-1} w (trans HC=CH); ^1H NMR (100 MHz) τ 0.22 (d, $J_{CHO,4'}$ = 8 Hz, CHO next to H-4'), 0.33 (d, $J_{CHO,2}$ = 8 Hz, CHO next to H-2), 2.21 (d, $J_{1,2}$ = 16 Hz, H-1), 2.05–3.32 (m, benzenoid H, H-1', H-2', H-3'), 3.33 (dd, $J_{2,1}$ = 16, $J_{2,CHO}$ = 8 Hz, H-2), 3.67 (dd, $J_{4',3'}$ = 16, $J_{4',CHO}$ = 8 Hz, H-4').

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 78.76; H, 5.78.

***o*-Formylcinnamaldehyde (19).** A solution of lithium methoxide, prepared by dissolving lithium (0.43 g, 62 mg-atoms) in absolute methanol (190 mL), was added dropwise over 3 h to a stirred solution of o-phthalaldehyde (**5**, 7.5 g, 56 mmol) and 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide[11] (26.4 g, 62 mmol) in dry DMF (300 mL) at 80–85 °C (bath) under a reflux condenser. After a further 30 min, the reaction mixture was cooled and poured onto water. The mixture was extracted with ether and the extracts were washed with water. Removal of solvent gave a dark, oily residue which was dissolved in THF (150 mL) and stirred with 10% hydrochloric acid (100 mL) for 1 h. The mixture was poured onto water and extracted with ether. The extracts were washed with saturated sodium bicarbonate solution and then with water. The semisolid mass remaining after solvent removal was extracted with ether (5 × 25 mL), and the combined extracts were evaporated. The dark, oily residue was then chromatographed on a column of silica gel (10 × 4 cm) with 35% ethyl acetate–pentane as eluent. The second compound eluted was the impure dialdehyde **19** which was rechromatographed as before. Crystallization from ethyl acetate–cyclohexane yielded pure **19** (1.58 g, 18%) as yellow needles: mp 62–63 °C; MS *m/e* 160 (M^+); IR ($CHCl_3$) 1690 s and 1670 s (C=O), 980 cm^{-1} s (trans HC=CH); ^1H NMR (60 MHz) τ −0.28 (s, CHO), 0.15 (d, $J_{CHO,2}$ = 8 Hz, unsaturated CHO), 1.40 (d, $J_{1,2}$ = 16 Hz, H-1), 1.8–2.5 (m, benzenoid H), 3.32 (dd, $J_{2,1}$ = 16, $J_{2,CHO}$ = 8 Hz, H-2).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.76; H, 4.98.

1-(Formylethenyl)-2-(4'-formyl-1',3'-butadienyl)benzene (18) from 19. A stirred solution of the dialdehyde **19** (1.55 g, 9.7 mmol) and carbethoxymethylenetriphenylphosphorane[9] (6.75 g, 19 mmol) in dichloromethane (70 mL) was heated under reflux for 19 h. The mixture was cooled, the solvents were evaporated, and the residue was extracted with ether (5 × 15 mL). The ether was evaporated and the residue was chromatographed on a column of silica gel (90 g) with 30% ethyl acetate–petrol as eluent. Early fractions afforded the diester **20** (2.3 g, 80%) as a yellow gum: ^1H NMR (60 MHz) τ 1.35 (d, $J_{1,2}$ = 16 Hz, H-1), 2.1–2.7 (m, benzenoid H, H-1', H-3'), 2.98 (dd, $J_{2',1'}$ = 16, $J_{2',3'}$ = 11 Hz, H-2'), 3.70 (d, $J_{4',3'}$ = 16 Hz, H-4'), 4.03 (d, $J_{2,1}$ = 16 Hz, H-2), 5.70 and 5.80 (each q, $CO_2CH_2CH_3$), 8.67 and 8.70 (each t, $CO_2CH_2CH_3$).

A solution of diisobutylaluminum hydride (4.58 g, 32 mmol) in dry benzene (23 mL) was added over 30 min to a stirred solution of the diester **20** (2.2 g, 7.3 mmol) in dry benzene (80 mL). The solution was stirred for 2 h, methanol (70 mL) was then added cautiously, and stirring was continued for a further 30 min. Filtration and evaporation led to the crude diol **17** (1.57 g) as a pale yellow solid.

A solution of the crude diol **17** (1.57 g) in dichloromethane (150 mL) was stirred with activated manganese dioxide[27] (14 g) for 4 h. Filtration through Celite, thorough washing with dichloromethane, evaporation, and crystallization from ethyl acetate afforded the dialdehyde **18** (0.97 g, 62% based on **20**) as yellow prisms, identical with that described above.

6,8-Bisdehydrobenz[16]annulene (9,10,11,12-Tetradehydrobenzocyclohexadecene, 25). The dialdehyde **18** (475 mg, 2.24 mmol) was allowed to react with the product obtained from propargyl bromide (1.19 g, 10 mmol), aluminum foil (180 mg, 6.67 mg-atoms), and mercuric chloride (40 mg), exactly as described above for the synthesis of **10.** This procedure led to the crude diol **21** (650 mg) as a nearly colorless oil: ^1H NMR (60 MHz) τ 2.3–4.4 (m, benzenoid and olefinic H), 5.55 (m, methine H), 7.2–7.6 (m, methylene and hydroxyl H), 7.90 (t, C≡CH).

A solution of the crude diol **21** (150 mg) in DMF (25 mL) was added dropwise over 1 h to a stirred solution of cupric acetate monohydrate (2.8 g) in DMF (100 mL) at 50–55 °C. After a further 1 h, the solution was cooled, poured onto a mixture of brine (150 mL) and 1 N hydrochloric acid (50 mL), and extracted well with ether. The ether extracts were washed well with water, and the solvent was evaporated. Chromatography on a short column of silicic acid (6 g), with 2% ethanol–chloroform as eluent, gave the crude macrocyclic diol **23** (110 mg) as a colorless solid: ^1H NMR (60 MHz) τ 2.3–4.5 (m, benzenoid and olefinic H), 5.55 (m, methine H), 7.0–7.6 (m, methylene H).

The crude diol **23** (250 mg, 0.86 mmol) was allowed to react with methanesulfonyl chloride (220 mg, 1.9 mmol) and triethylamine (200 mg, 2 mmol) in DME (11 mL) at 0 °C, followed by treatment of the filtrate with DBN (260 mg, 2.1 mmol) in DME (1.5 mL), exactly as described above for the conversion of **12** to **14.** The resulting product was chromatographed on a column of alumina (4 × 2 cm) with benzene as eluent. Crystallization from hexane gave the benz[16]annulene **25** (157 mg, 53% based on **18**) as brick-red needles: mp 98–99 °C; UV (Et_2O) λ_{max} 267 nm sh (ϵ 17 100), 280 sh (36 500), 297 (61 400), 305 sh (59 100), 442 (700); IR ($CHCl_3$) 2200 w (C≡C), 990 cm^{-1} s (trans HC=CH); ^1H NMR (100 MHz) τ 0.14 (dd, $J_{3,2}$ = 16, $J_{3,4}$ = 11 Hz, H-3), 0.20 (dd, $J_{13,12}$ = 16, $J_{13,14}$ = 11 Hz, H-13), 0.82 (d, $J_{15,14}$ = 16 Hz, H-15), 2.8–3.3 (m, H^X, $H^{X'}$, H^Y, $H^{Y'}$), 3.6–4.0 (m, H-2, H-4, H-11, H-14), 4.35 (dd, $J_{12,13}$ = 16, $J_{12,11}$ = 6 Hz, H-12), 4.94 and 4.98 (each d, $J_{5,4}$ = $J_{10,11}$ = 11 Hz, H-5, H-10).

Anal. Calcd for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.39; H, 5.69.

5,10-Dimethyl-6,8-bisdehydrobenz[16]annulene (8,13-Dimethyl-9,10,11,12-tetradehydrobenzocyclohexadecene, 26). The dialdehyde **18** (400 mg, 1.89 mmol) was allowed to react with the product obtained from 3-bromo-1-butyne[14] (1.5 g, 11.4 mmol), magnesium (270 mg, 11.1 mg-atoms), and mercuric chloride (20 mg), exactly as described above for the synthesis of **11.** This procedure yielded the crude diol **22** (580 mg) as a yellow oil.

A solution of crude **22** (580 mg) in DMF (20 mL) was added dropwise over 2 h to a stirred solution of cupric acetate monohydrate (10 g) in DMF (200 mL) at 60 °C. After a further 2 h, the solution was cooled, poured onto water (1 L), and extracted with ether. The ether extracts were washed well with water, and the solvent was evaporated. The resulting crude macrocyclic diol **24** (490 mg) was obtained as a yellow powder.

The crude diol **24** (490 mg, 1.5 mmol) was allowed to react with methanesulfonyl chloride (430 mg, 3.8 mmol) and triethylamine (480 mg, 4.8 mmol), followed by treatment of the filtrate with DBN (1.4 g, 11.3 mmol), exactly as described above for the conversion of **13** to **2.** Chromatography of the product on a column of alumina (8 × 4 cm), elution with petrol, and crystallization from this solvent gave the benz[16]annulene **26** (95 mg, 18% based on **18**) as red needles: mp 133–134 °C; MS *m/e* 282.142 (M^+, calcd 282.141); UV (Et_2O) λ_{max} 265 nm sh (ϵ 18 600), 278 sh (40 100), 298 (81 500), 308 sh (77 500), 426 (4300); IR (KBr) 2180 w (C≡C), 978 s and 974 cm^{-1} s (trans HC=CH); ^1H NMR (220 MHz) τ 0.55 (dd, $J_{3,2}$ = 16, $J_{3,4}$ = 10 Hz, H-3), 0.58 (dd, $J_{13,12}$ = 15, $J_{13,14}$ = 11 Hz, H-13), 1.10 (d, $J_{15,14}$ = 15 Hz, H-15), 2.9–3.2 (m, H^X, $H^{X'}$, H^Y, $H^{Y'}$), 3.80 (dd, $J_{14,15}$ = 15, $J_{14,13}$ = 11 Hz, H-14), 3.89 (d, $J_{2,3}$ = 16 Hz, H-2), 3.93 (d, $J_{4,3}$ = 10 Hz, H-4), 4.06 (d, $J_{11,12}$ = 6 Hz, H-11), 4.27 (dd, $J_{12,13}$ = 15, $J_{12,11}$ = 6 Hz, H-12), 8.30 [s(b), CH_3-5, CH_3-10].

1,2-Bis(4-formyl-1,3-butadienyl)benzene (30). A solution of o-phthalaldehyde (**5**, 8.97 g, 0.067 mol) in dichloromethane (50 mL) was added dropwise over 30 min to a vigorously stirred solution of the ylide 27[20] (50 g, 0.134 mmol) in dichloromethane (400 mL), which was boiled under reflux. After a further 2 h of refluxing, the solution was cooled and stirred for 20 h at ambient temperature. The residue after solvent removal was extracted with ether (5 × 75 mL), and the extracts were evaporated. Chromatography of the resultant red oil on a column of silica gel (12 × 6 cm) with 30% ethyl acetate–pentane as eluent afforded the diester **28** (stereoisomeric mixture, 18.0 g, 82%) as a yellow oil: ^1H NMR (60 mhz) τ 2.2–4.4 (m, benzenoid and olefinic H), 5.79 and 5.85 (each q, $CO_2CH_2CH_3$), 8.72 and 8.78 (each t, $CO_2CH_2CH_3$).

A solution of diisobutylaluminum hydride (15.62 g, 0.11 mol) in dry benzene (78 mL) was added dropwise over 30 min to a stirred solution of the stereoisomeric diester **28** (8.1 g, 0.025 mol, dried by azeotropic distillation with benzene) in dry benzene (300 mL). The solution was stirred for a further 18 h, and methanol (250 mL) was then added

cautiously, followed by concentrated sulfuric acid (10 drops). The mixture was stirred for 15 min, filtered, and evaporated. This procedure yielded the crude stereoisomeric diol **29** (6.0 g) as a yellow oil: ^{1}H NMR (60 MHz) τ 2.4–4.4 (m, benzenoid and olefinic H), 5.88 (m, CH_2), 7.50 (m, OH).

The crude diol **29** (14.0 g) in dichloromethane (1.1 L) was stirred with activated manganese dioxide[27] (128 g) for 23 h. The mixture was filtered through Celite, and the solid was washed well with dichloromethane. The combined filtrates were concentrated to ~500 mL, a crystal of iodine was added, and the solution was allowed to stand at ambient temperature for 18 h. The solution was then washed with dilute sodium thiosulfate solution, dried, and evaporated. Crystallization from dichloromethane–petrol afforded the all-trans dialdehyde **30** (4.7 g, 34% based on **28**) as bright yellow blades: mp 159–160 °C; MS *m/e* 238 (M^+); UV (Et_2O) λ_{max} 297 nm (ϵ 47 600), 340 (42 500); IR ($CHCl_3$) 1680 s (C=O), 1620 s (C=C), 990 cm^{-1} s (trans HC=CH); ^{1}H NMR (60 MHz) τ 0.30 (d, $J_{CHO,4}$ = 8 Hz, CHO), 2.2–3.3 (m, benzenoid H, H-1, H-2, H-3), 3.52 (dd, $J_{4,3}$ = 16, $J_{4,CHO}$ = 8 Hz, H-4).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.49; H, 5.97.

8,10-Bisdehydrobenz[18]annulene (11,12,13,14-Tetradehydrobenzocyclooctadecene, 35). The dialdehyde **30** (1.6 g, 6.72 mmol) was allowed to react with the product obtained from propargyl bromide (3.6 g, 30 mmol), aluminum foil (540 mg, 20 mg-atoms), and mercuric chloride (120 mg), exactly as described above for the synthesis of **10**. Chromatography of the product on a column of silicic acid (5 × 4 cm) and elution with chloroform gave the diol **31** (2.1 g, 98%) as a pale yellow solid: ^{1}H NMR τ 2.4–4.4 (m, benzenoid and olefinic H), 5.58 (m, methine H), 7.3–7.7 (m, methylene and hydroxyl H), 7.90 (t, C≡CH).

A solution of the diol **31** (318 mg, 1 mmol) in DMF (50 mL) was added dropwise over 1 h to a stirred solution of cupric acetate monohydrate (6.0 g) in DMF (250 mL) at 55 °C. After a further 1 h, the solution was cooled, poured onto brine (600 mL), and extracted with ether. The ether extracts were washed well with water, and the solvent was evaporated. Chromatography on a column of silicic acid (3 × 2 cm) and elution with chloroform afforded the macrocyclic diol **33** (115 mg, 36%) as a nearly colorless solid.

The diol **33** (240 mg, 0.76 mmol) was allowed to react with methanesulfonyl chloride (180 mg, 1.6 mmol) and triethylamine (170 mg, 1.7 mmol) at 0 °C, followed by treatment of the filtrate with DBN (210 mg, 1.7 mmol), exactly as described above for the conversion of **12** to **14**. The resulting product was chromatographed on a column of alumina (5 × 3 cm) with benzene as eluent. Crystallization from benzene–hexane yielded the benz[18]annulene **35** (126 mg, 59%) as long, dark red needles: mp >200 °C dec; MS *m/e* 280.125 (M^+, calcd 280.125); UV (Et_2O) λ_{max} 298 nm sh (ϵ 18 500), 339 (68 700), 410 sh (7600); IR ($CHCl_3$) 2200 w (C≡C), 985 s and 970 cm^{-1} m (trans HC=CH); ^{1}H NMR (100 MHz) τ 1.90 (m, H^X), 2.49 (m, H^Y), 2.5–2.9 (m, H-3, H-6, H-13, H-16), 3.06 (dd, $J_{4,5} = J_{15,14}$ = 16, $J_{4,3} = J_{15,16}$ = 8 Hz, H-4, H-15), 3.83 (d, $J_{7,6} = J_{12,13}$ = 10 Hz, H-7, H-12), 4.80 (d, $J_{2,3} = J_{17,16}$ = 16 Hz, H-2, H-17), 4.90 (dd, $J_{5,4} = J_{14,15}$ = 16 Hz, $J_{5,6} = J_{14,13}$ = 11 Hz, H-5, H-14).

7,12-Dimethyl-8,10-bisdehydrobenz[18]annulene (10,15-Dimethyl-11,12,13,14-tetradehydrobenzocyclooctadecene, 36). The dialdehyde **30** (400 mg, 1.68 mmol) was allowed to react with the product obtained from 3-bromo-1-butyne[14] (1.8 g, 13.6 mmol), magnesium (320 mg, 13.2 mg-atoms), and mercuric chloride (50 mg), exactly as described above for the synthesis of **11**. The resulting crude diol **32** (580 mg) was a yellow gum.

A solution of the crude diol **32** (580 mg) in pyridine (20 mL) was added dropwise over 3 h to a stirred solution of anhydrous cupric acetate[15] (4.0 g) in pyridine (160 mL) and ether (40 mL) at 50 °C. After a further 30 min, the solution was cooled and the solvent was evaporated. Water was added to the residue, the mixture was extracted with ether, and the extracts were washed with water. Evaporation of the solvent led to the crude macrocyclic diol **34** (270 mg) as a brown froth.

The crude diol **34** (270 mg) was allowed to react with methanesulfonyl chloride (390 mg, 3.4 mmol) and triethylamine (340 mg, 3.4 mmol), and the filtrate was then treated with DBN (1.2 g, 9.7 mmol), exactly as described above for the conversion of **13** to **2**. Chromatography of the product on a column of alumina (6 × 4 cm), elution with 10% ether–petrol, and crystallization from dichloromethane–petrol gave the benz[18]annulene **36** (57 mg, 11% based on **30**) as orange prisms or needles: mp 214–216 °C; MS *m/e* 308 (M^+); UV (Et_2O) λ_{max} 283 nm sh (ϵ 13 300), 298 sh (18 300), 342 (64 600), 408 sh (9600); ^{1}H NMR (100 MHz) τ 1.94 (m, M^X), 2.58 (m, H^Y), 2.76 (dd, $J_{3,2} = J_{16,17}$ = 16, $J_{3,4} = J_{16,15}$ = 7 Hz, H-3, H-16), 2.83 (d, $J_{6,5} = J_{13,14}$ = 11 Hz, H-6, H-13), 3.15 (dd, $J_{4,5} = J_{15,14}$ = 16, $J_{4,3} = J_{15,16}$ = 7 Hz, H-4, H-15), 4.77 (d, $J_{2,3} = J_{17,16}$ = 16 Hz, H-2, H-17), 5.06 (dd, $J_{5,4} = J_{14,15}$ = 16, $J_{5,6} = J_{14,13}$ = 11 Hz, H-5, H-14), 7.72 (s, CH_3).

Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.12; H, 6.47.

1-(4-Formyl-1,3-butadienyl)-2-(6′-formyl-1′,3′,5′-hexatrienyl)benzene (39). A solution of the dialdehyde **18** (510 mg, 2.4 mmol) in dichloromethane (15 mL) was added dropwise over 15 min to a stirred solution of carbethoxymethylenetriphenylphosphorane[9] (1.7 g, 4.9 mmol) in dichloromethane (20 mL). The solution was then boiled under reflux for 5 h and cooled, and the solvent was evaporated. The residue was extracted with ether (4 × 10 mL), and the solvent was evaporated. Chromatography of the residue on a column of silica gel (5 × 3 cm) with 30% ethyl acetate–pentane as eluent gave the diester **37** (790 mg, 93%) as a bright yellow oil: ^{1}H NMR (60 MHz) τ 2.0–4.3 (m, benzenoid and olefinic H), 5.76 (q, $CO_2CH_2CH_3$), 8.68 (t, $CO_2CH_2CH_3$).

A solution of diisobutylaluminum hydride (1.42 g, 10 mmol) in dry benzene (8 mL) was added dropwise over 15 min to a stirred solution of the diester **37** (790 mg, 2.2 mmol) in dry benzene (25 mL). After a further 1 h, methanol (25 mL) was added cautiously and stirring was continued for 15 min. The mixture was filtered, the solid was washed with methanol, and the solvent was evaporated. The resulting crude diol **38** (550 mg, 91%) was a pale yellow solid.

The crude diol **38** (550 mg) in dichloromethane (65 mL) was stirred with activated manganese dioxide[27] (5 g) for 2 h. The mixture was filtered through Celite, and the solid was washed well with dichloromethane. Evaporation and crystallization from ethyl acetate–cyclohexane gave the dialdehyde **39** (405 mg, 75%; 64% based on **18**) as yellow-orange needles: MS *m/e* 264.114 (M^+, calcd 264.115); IR ($CHCl_3$) 1670 s (C=O), 1620 m (C=C), 995 cm^{-1} m (trans HC=CH); ^{1}H NMR (60 MHz) τ 0.34 (d, J = 8 Hz, CHO), 0.41 (d, J = 8 Hz, CHO), 2.2–4.0 (m, benzenoid and olefinic H).

8,10-Bisdehydrobenz[20]annulene (11,12,13,14-Tetradehydrobenzocycloeicosene, 41). The dialdehyde **39** (360 mg, 1.4 mmol) was allowed to react with the product obtained from propargyl bromide (740 mg, 6.2 mmol), aluminum foil (110 mg, 4.1 mg-atoms), and mercuric chloride (25 mg), exactly as described above for the synthesis of **10**. The resulting crude diol **40** (430 mg) was obtained as a yellow glass: ^{1}H NMR τ 2.2–4.4 (m, benzenoid and olefinic H), 5.61 (m, methine H), 7.2–7.7 (m, methylene and hydroxyl H), 7.90 (t, C≡CH).

A solution of the crude diol **40** (320 mg) in DMF (90 mL) was added dropwise over 2 h to a stirred solution of cupric acetate monohydrate (8.4 g) in DMF (300 mL) at 60 °C. After a further 45 min, the solution was cooled, poured onto a mixture of brine (350 mL), 10% hydrochloric acid (200 mL), and ice, and extracted with ether. The extract was washed with water (7 × 50 mL) and sodium bicarbonate solution, and was then evaporated. The resulting crude macrocyclic diol (225 mg, pale yellow solid) was allowed to react with methanesulfonyl chloride (170 mg, 1.5 mmol) and triethylamine (160 mg, 1.6 mmol) at 0 °C, followed by treatment of the filtrate with DBN (200 mg, 1.6 mmol), exactly as described above for the conversion of **12** to **14**. Chromatography of the product on a column of alumina (4 × 2 cm), elution with benzene, and crystallization from benzene–hexane yielded the benz[20]annulene **41** (61 mg, 20% based on **39**) as dark purple brown prisms: mp >120 °C dec; MS *m/e* 306.141 (M^+, calcd 306.141); UV (Et_2O) λ_{max} 301 nm sh (ϵ 53 200), 324 (95 300), 334 (93 400), 434 (2100), with absorption >550 nm; ^{1}H NMR (100 MHz) τ 1.0–1.8 (m, 5 H, inner olefinic H), 2.8–3.2 (m, 4 H, benzenoid H), 3.5–4.2 (m, 7 H, outer olefinic H except H-7, H-12), 4.95 [d(b), 2 H, $J_{7,6} = J_{12,13}$ = 11 Hz, H-7, H-12].

Acknowledgment. Financial support from the Science Research Council and the Royal Society is gratefully acknowledged.

Registry No.—**5,** 643-79-8; **6,** 28839-73-8; **7,** 61650-41-7; **8,** 61650-42-8; **9,** 61650-43-9; **10,** 61650-44-0; **11,** 61650-45-1; **12,** 61650-46-2; **13,** 61650-47-3; **15,** 61650-48-4; **16,** 61650-49-5; **17,** 61650-50-8; **18,** 61650-51-9; **19,** 61650-52-0; **20,** 61650-53-1; **21,** 61650-54-2; **22,** 61650-55-3; **23,** 61650-56-4; **24,** 61650-57-5; **27,** 51544-70-8; **28,** 61650-58-6; **29,** 61650-59-7; **30,** 61650-60-0; **31,** 61650-61-1; **32,** 61650-62-2; **33,** 61650-63-3; **34,** 61650-64-4; **37,** 61675-25-0; **38,** 61650-65-5; **39,** 61650-66-6; **40,** 61650-67-7; carbethoxymethylenetriphenylphosphorane, 1099-45-2; 1,3-dioxolan-2-ylmethyltriphenylphosphonium bromide, 52509-14-5; propargyl bromide, 106-96-7; methanesulfonyl chloride, 124-63-0; 3-bromo-1-butyne, 18668-72-9; triethyl phosphonoacetate, 867-13-0.

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Acid-Catalyzed Cyclialkylation of Benzene with Isoprene

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The acid-catalyzed reaction of isoprene with benzene forms a more complex mixture of reaction products than previously observed from alkylbenzenes. The formation of identified products is rationalized through existing carbonium ion theory. These products include 1,1-dimethylindan, the majority of the possible tetramethylhydrindacenes, both hexamethyltrindans, and two isopentyltetramethylhydrindacenes. Synthesis through independent routes provided standards for identification of products and study of intermediates.

The acid-catalyzed cyclialkylation of benzenoid hydrocarbons is well known.[2a] Such reaction with isoprene is a convenient and direct route to substituted 1,1-dimethylindans and tetramethylhydrindacenes. While an array of products are observed with mono- and dialkylbenzenes, the reaction can provide a reasonably clean product or product mixture from which several pure hydrocarbons have been isolated.[2b-e] Hydrocarbons **1**, **2**, and **7** were readily isolated in the current work and appear as major peaks in the GC trace shown in Figure 1.

Cyclialkylation products have been considered to have potential as high-energy fuels[2d,3a] and source materials in medicine[3b] and perfumery.[4] Acetylated and nitrated derivatives show musk properties.[4] Acetylation also yields ketones active as preemergence herbicides.[5]

The cyclialkylation of benzene with isoprene is not a useful reaction for the preparation of 1,1-dimethylindan (**1**)[6] in quantity, since this is rapidly converted to the hydrindacenes as shown in Scheme I. Schmerling[2b] first observed that the yield of **2** exceeds that of **1**.

Despite the low yields of **1** and **2**, we decided to use the cyclialkylation reaction for their preparation and a concomitant study of the cyclialkylation process in which **1** is regarded as an isolable but reacting intermediate.

A trial cyclialkylation reaction (procedure A) gave the expected low yields of **1** (3.5%) and **2** (9–10%). A second run (procedure A) in which the amounts of reagents were increased 20-fold showed a decreased yield of **1**, which results from the increased time necessary for addition of isoprene, and consequent conversion of **1** to other products.

The preparation of **1** in larger quantity was required to determine its role as an intermediate. Since increasing the scale of the preparation was unsatisfactory, we carried out numerous successive small runs (procedure B) involving rapid mixing of reagents, quenching, and workup of the reaction mixture. By this means we were able to accumulate a substantial quantity of **1**.[6] The other products from this preparation were thus also available for study. Distillation of the product mixture afforded the crystalline tetramethylhydrindacene **2** and the crystalline *as*-hexamethyltrindan **7**. Preparative GC was used to isolate **6**,[7a] **9**,[7b] and *tert*-butylbenzene (**11**).[7b] Their structures, along with those of **2** and **7**, were established by spectroscopic studies.

It is assumed that **9** is derived by an isopentenylation of **6**

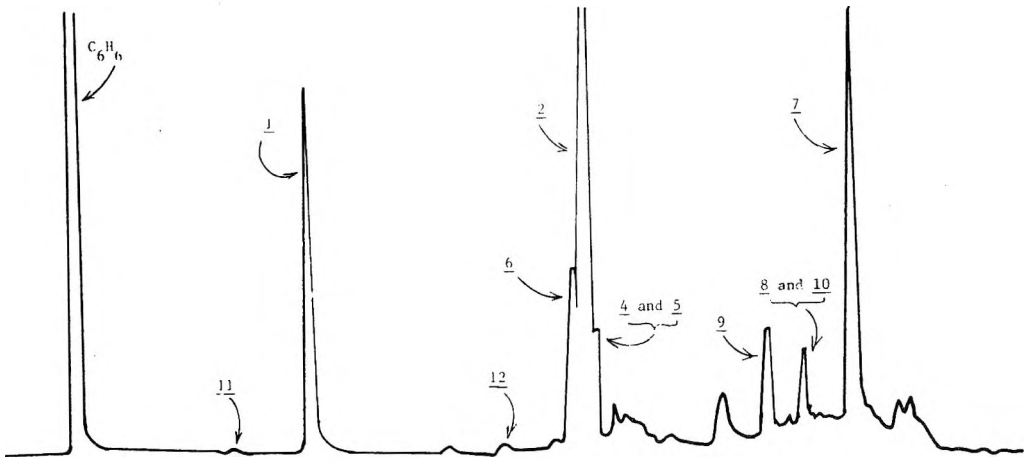
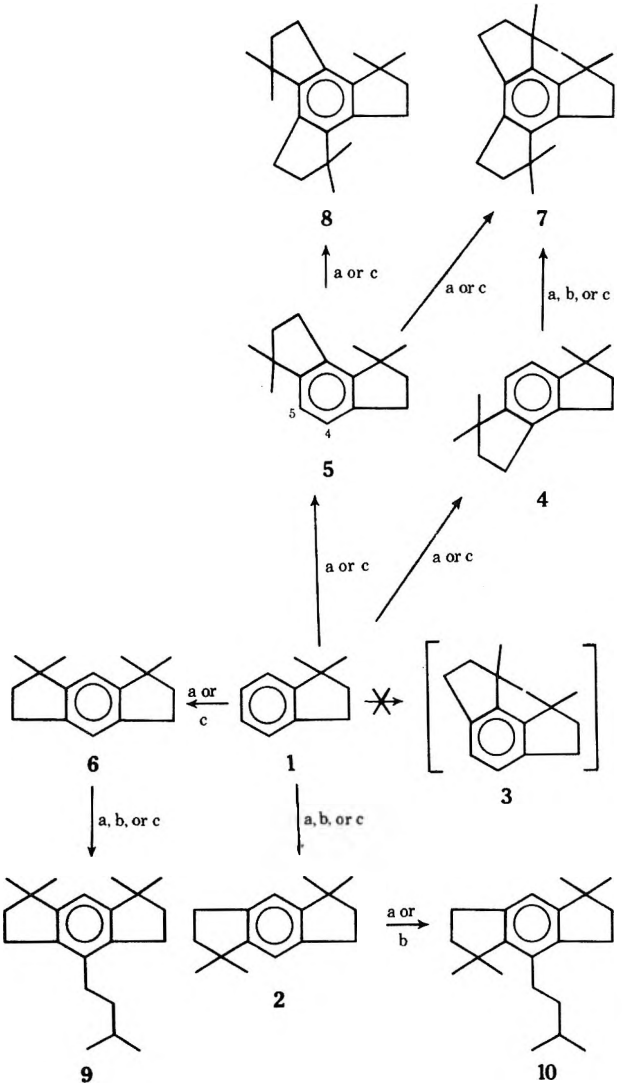


Figure 1. Programmed-temperature GC of distilled cyclialkylation products.

Scheme I



a, benzene, isoprene, sulfuric acid; b, isoprene, trifluoroacetic acid, sulfuric acid in petroleum ether; c, isoprene, sulfuric acid.

with subsequent hydrogenation of the side chain through protonation and hydride acquisition as previously observed.[2c] Once **11** had been identified, it was assumed that 6-*tert*-butyl-1,1-dimethylindan (**12**) would be present.[2c,d] This was confirmed by GC comparison (Figure 1) with authentic material. The formation of *tert*-butylbenzene may be rationalized as due to acid-catalyzed degradation of isoprene to a C_4 moiety.[8a,b]

The GC trace of the reaction product mixture from this cyclialkylation is complex. The trace[9a] shown in Figure 1 is substantially more complicated than that of product mixtures from mono- or dialkylbenzenes.[2c] The complexity of this mixture and the difficulty encountered in isolating pure compounds prompted the synthesis of **4, 5, 6, 8,** and **10** to determine whether these hydrocarbons were represented by GC peaks of Figure 1 and whether **2, 4, 5,** and **6** could serve as reaction intermediates.

Syntheses of **2, 4, 5,** and **6** involved use of the acid-catalyzed cyclialkylation process applied to specifically prepared intermediates as shown in Scheme II. Amberlyst-15, a sulfonic acid resin, was found to be the most effective and convenient reagent for these cyclizations.[10]

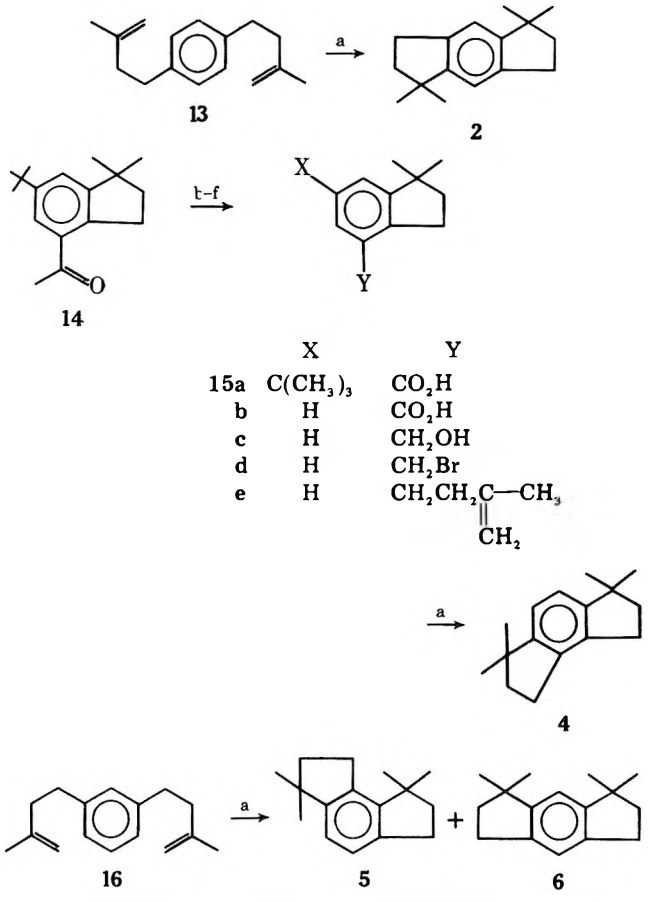
An added reason to synthesize **2** from the diene **13** was to determine whether cyclization would be exclusively to **2** or the less sterically favored **3** would result. The absorptions of the *gem*-methyl groups of **2** appear at δ 1.21 as a singlet. If **3** were present in the reaction mixture, *gem*-methyl absorption should be in the δ 1.3–1.4 range, as it is for the hindered methyl groups of **7**. When NMR data were obtained at intervals during the reaction, these low-field *gem*-methyl absorptions were not observed. Our GC and NMR data also indicate that the pendant double bonds of **13** are first shifted to become trisubstituted. This was established by comparing shift values of vinyl and allylic protons during the course of the reaction with those of 2-methyl-4-phenyl-2-butene.[6] Hence, **3** is probably not formed and therefore not a precursor to **7**.

The synthesis of **4** from 4-acetyl-6-*tert*-butyl-1,1-dimethylindan (**14**) via 1,1-dimethyl-4-hydroxymethylindan (**15c**)[4b] was accomplished in 20% overall yield. Gas chromatography comparisons[9b] showed **4** to be one of the minor peaks of the tetramethylhydrindacene fraction shown in Figure 1.

Cyclization[6,10] of 1,3-bis(3-methyl-3-butenyl)benzene (**16**) prepared by the Grignard process of Theimer and Blumenthal[4d] gave a 1:1 mixture of **5** and **6**. These were separated by distillation.[11] Comparison of the NMR spectra of **6** obtained from cyclialkylation and **6** made by synthesis as shown in Scheme II established the identity of the former. The purified **5** and **6** were individually mixed with the tetramethylhydrindacene fraction of the cyclialkylation products, and their presence in this mixture was established by using capillary GC.[9b] The order of elution and the peak ratios on the capillary column were **6:5:4:2** (3:1:2:12).

The synthesis of *s*-hexamethyltrindan (**8**) was accomplished as shown in Scheme III. This allowed a comparison of the GC trace of pure **8** with Figure 1 and thus identification of another of the GC peaks. We also synthesized **10** by acylation of **2**,

Scheme II



a, Amberlyst-15, cyclohexane, Δ; b, OBr^-, H_3O^+; c, $AlCl_3$, toluene; d, $(i\text{-}C_4H_9)_2AlH$, C_6H_6; e, HBr; f, methallylmagnesium chloride, ether.

reduction of the resulting ketone, dehydration, and catalytic hydrogenation as shown in Scheme IV.

In Figure 1, **8** and **10** show the same retention time. However, the mixture was resolved to give **8**:**10** (1:3) by using a "Scot" capillary GC column.[9c]

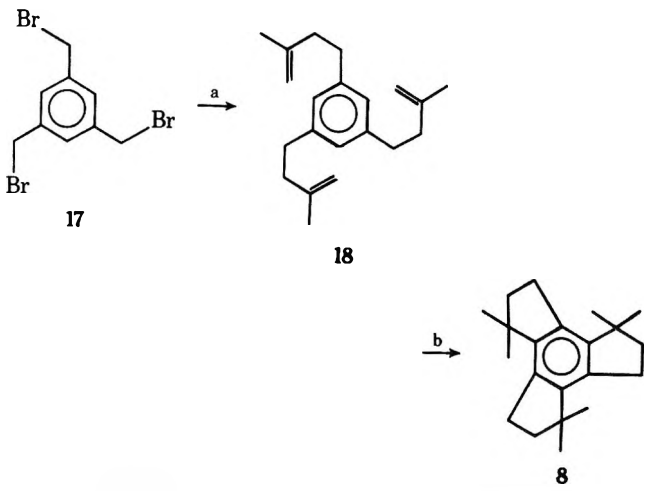
To establish the relationship of **1** and the tetramethylhydrindacenes **2, 4, 5,** and **6** as intermediates to **7, 8, 9,** and **10** shown in Figure 1, we sought reaction conditions not requiring benzene as solvent. Isoprene added to a mixture of trifluoroacetic acid, petroleum ether, and sulfuric acid caused a low-yield conversion of **2** to **10** and **6** to **9.** In addition, it provided **7** from **4** but did not yield **7** or **8** from **5.**

When isoprene was added to sulfuric acid and a solvent (petroleum ether, cyclohexane, chlorobenzene, or methanesulfonic acid) containing **2, 4, 5,** or **6,** no useful products were obtained. However, treatment of isoprene solutions of **2, 4, 5,** and **6** with sulfuric acid at 0 °C resulted in the formation of **7** from **4, 7** and **8** from **5,** and **9** from **6.** Isopentylation of **2** under these conditions did not occur.

Chromic acid oxidation to ketones at the benzylic position[12] was used to obtain supporting evidence for the structures of **4, 7, 8,** and **9.** Of this series, **4** gave one monooxo and one dioxo derivative. Trindan **7** would be expected to give three monooxo, three dioxo, and one trioxo derivatives, whereas trindan **8** would yield one monooxo, one dioxo, and one trioxo derivative. The GC data showed the expected number of products for **7** and **8.** The oxidation of **9** yielded monooxo and dioxo derivatives, mp 84–86 and 194–195 °C, respectively. The ^1H NMR data show that the benzylic protons of the isopentyl group survive the oxidation.

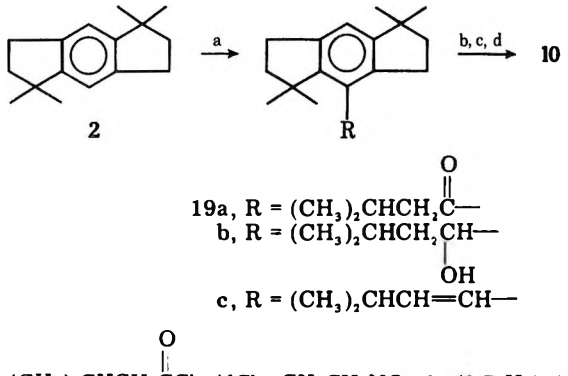
The synthesized hydrocarbon standards **2**,[9b] **4**,[9b] **5**,[9b] **6**,[9b] **8**,[9c] and **10**[9c] were used to identify GC peaks.

Scheme III



a, methallylmagnesium chloride, ether; b, A-15, cyclohexane, Δ.

Scheme IV



a, $(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}Cl$, $AlCl_3$, $CH_3CH_2NO_2$; b, $(i\text{-}C_4H_9)_2AlH$, C_6H_6; c, Amberlyst-15, C_6H_6; d, H_2, Pd/C, C_2H_5OH.

Experimental Section[13]

Cyclialkylation of Benzene with Isoprene in the Presence of Sulfuric Acid. Procedure A. To a 1-L, three-necked, round-bottom flask equipped with stirrer and dropping funnel and cooled in an ice bath were added 249 g (3 mol) of benzene and 50 mL (0.51 mol) of 85% sulfuric acid followed by 68 g (1.0 mol) of isoprene in 102 g (1.3 mol) of benzene over 16 min at 15–20 °C. Stirring was continued for 15 min. The red-brown sulfuric acid layer was withdrawn, and the benzene layer was washed with 30 mL of water, with aqueous sodium carbonate, and 2 × 50 ml of water, and dried ($MgSO_4$). Concentration and distillation gave **1** (3.5%).

A second run was made with the scale increased 20-fold and the addition time increased from 16 to 135 min. Distilled product consisted of 100 g (2.3%) of **1,** 305 g (9.5%) of crude **2,** a liquid fraction weighing 216 g, and a final fraction (178 g, 6%), bp 160–220 °C (1 mm), of mainly **7.**

Procedure B. A 5-L, indented, round-bottom flask equipped with a dropping funnel, Lightnin XP stirrer, and turbine stirring paddle was cooled to 10 °C in a stirred ice–water–salt bath, and 950 g (12.2 mol) of benzene and 100 mL of 97% sulfuric acid were added. Isoprene (286 g, 4.77 mol) diluted with 492 g (6.3 mol) of benzene was then added as rapidly as the temperature increase permitted (max 20 °C). The total addition time was 3–5 min. The stirrer was stopped and the flask contents were rapidly pumped with a Randolph Model 610 peristaltic pump into a 12-L separatory funnel. After 10 min, the lower "red oil" layer was drained off and the separatory funnel contents were then poured directly onto anhydrous sodium carbonate. The dried material was filtered, combined with that from other runs, and distilled to give **1, 2,** and **7** in 8, 7, and 13% yields, respectively.

1,1-Dimethylindan (**1**)[6] was redistilled: bp 73 °C (3 mm) (lit.[14] 189–191 °C); mass spectrum (70 eV) *m/e* (rel intensity) 146 (M^+, 13) 132 (5), 131 (100), 116 (8), 115 (13), 91 (15); ^1H NMR (CCl_4) δ 7.05 (s, 4, ArH), 2.85 (t, 2, $ArCH_2$–), 1.88 [t, 2, $ArC(CH_3)_2CH_2$–], 1.24 [s, 6, $ArC(CH_3)_2$–].

A higher boiling fraction (bp 120–160 °C at 1 mm) yielded solid 1,1,5,5-tetramethyl-*s*-hydrindacene (**2**) which was filtered out and recrystallized from petroleum ether:[13] mp 95–96 °C (lit.[2a] 91–93 °C); mass spectrum (70 eV) *m/e* (rel intensity) 214 (M^+, 15), 200 (17), 199 (100), 143 (24), 128 (8), 92 (10); ^1H NMR (CCl_4) δ 6.79 (s, 2, ArH), 2.79 (t, 4, $ArCH_2$–), 1.86 [t, 4, $ArC(CH_3)_2CH$–], 1.21 [s, 12, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.61; H, 10.40.

The second fraction (bp 160–220 °C at 1 mm) yielded crystalline 1,1,4,4,9,9-hexamethyl-*as*-trindan (**7**). Recrystallization from 95% ethanol, acetone, and petroleum ether[13] and chromatography on acidic alumina with petroleum ether[13] gave pure **7**: mp 108–110 °C; mass spectrum (70 eV) *m/e* (rel intensity) 282 (M^+, 20), 268 (76), 267 (100), 211 (24), 181 (9), 126 (11); ^1H NMR (CCl_4) δ 2.81 (t, 2, $ArCH_2$–), 2.69 (t, 4, $ArCH_2$–), 1.81 (t, 6, $ArCH_2CH_2$–), 1.39 [s, 12, $ArC(CH_3)_2$–], 1.29 [s, 6, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{21}H_{30}$: C, 89.29; H, 10.71. Found: C, 89.50; H, 10.70.

Preparative GC Purification of 1,1,7,7-Tetramethyl-*s*-hydrindacene (6) and 4-Isopentyl-1,1,7,7-tetramethyl-*s*-hydrindacene (9). A liquid tetramethylhydrindacene fraction subjected to preparative GC separation[7a] gave crystalline **6**. Recrystallization from acetone and then with cold ether gave pure **6**: mp 60–61 °C (lit.[4d] 45–47 °C); mass spectrum (70 eV) *m/e* (rel intensity) 214 (M^+, 20), 200 (18), 199 (100), 143 (26), 41 (11), 29 (11); ^1H NMR (CCl_4) δ 6.84 (s, 1, ArH), 6.75 (s, 1, ArH), 2.76 (t, 4, $ArCH_2$–), 1.85 [t, 4, $ArC(CH_3)_2CH_2$–], 1.21 [s, 12, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.56; H, 10.33.

The fraction (bp 120–160 °C, 1 mm) containing the tetramethylhydrindacenes was dissolved in petroleum ether[13] and flushed through layers of silica gel, basic alumina, and acidic alumina until a colorless solution was obtained. Concentration followed by preparative GC[7a] separated **9** from the mixture as a yellow oil with 10% impurity. Hydrocarbon **9** slowly crystallized from the oil. Recrystallization from petroleum ether[13] gave waxy crystals of **9**: mp 46–47 °C; mass spectrum (70 eV) *m/e* (rel intensity) 284 (M^+, 13) 270 (22), 269 (100), 243 (28), 241 (34), 229 (23); ^1H NMR (CCl_4) δ 6.58 (s, 1, ArH), 2.76 (t, 4, $ArCH_2$–), 2.40 (t, 2, $ArCH_2$–), 1.86 [t, 4, $ArC(CH_3)_2CH_2$–], 1.63 [m, 1, $(CH_3)_2CH$–], 1.45 [m, 2, $ArCH_2CH_2CH(CH_3)_2$], 1.20 [s, 12, $ArC(CH_3)_2$–], 0.96 [d, 6, $(CH_3)_2CH$–].

Anal. Calcd for $C_{21}H_{32}$: C, 88.66; H, 11.34. Found: C, 88.71; H, 11.31.

Chromic Acid Oxidation of 1, 2, 6, 7, and 9. Chromic acid oxidation in acetic acid gave the previously described monoketones from **1**, **2**, and **6**.[12] Chromic acid oxidation of **7** gave a mixture of ketones which showed seven GC[9a] peaks (three monoketones, three diketones, and one triketone are possible). Preparative GC[7c] and recrystallization from petroleum ether[13] gave a monoketone: mp 136–138 °C; IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 2.73 (t, 4, $ArCH_2$–), 2.41 (s, 2, $ArCOCH_2$–), 1.92 (t, 4, $ArCH_2CH_2$–), 1.53, 1.45, and 1.40 [3, s, 18, $ArC(CH_3)_2$–].

Oxidation of **9** gave two products (mono- and diketone) separated by preparative GC.[7b] NMR studies showed that the side chain was not attacked in the oxidation. The monoketone from **9** showed mp 84–86 °C; IR (KBr) 1697 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 298 (M^+, 20), 256 (20), 255 (100), 242 (50), 227 (53), 43 (16); ^1H NMR (CCl_4) δ 6.91 (s, 1, ArH), 2.96. 2.82 (t, 4, $ArCH_2$–), 2.41 (s, 2, $ArCOCH_2$–), 1.91 (t, 2, $ArCH_2CH_2$–), 1.70 [m, 1, $(CH_3)_2CHCH_2$–], 1.37 [s, 6, $ArC(CH_3)_2$–], 1.35 [t, 2, $(CH_3)_2CHCH_2$–], 1.27 [s, 6, $ArC(CH_3)_2$–], 1.02, 0.92 [d, 6, $(CH_3)_2CH$–].

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.39; H, 10.30.

The diketone from **9** showed mp 194–195 °C; IR (KBr) 1695 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 312 (M^+, 28), 270 (23), 269 (100), 257 (17), 256 (87), 241 (42); ^1H NMR (CCl_4) δ 7.22 (s, 1, ArH), 3.30 (t, 2, $ArCH_2$–), 2.49 (s, 4, $ArCOCH_2$–), 1.70 [m, 1, $(CH_3)_2CHCH_2$–], 1.42 [s, 12, $ArC(CH_3)_2$–], 1.30 [t, 2, $(CH_3)_2CHCH_2$–], 1.27 [s, 6, $ArC(CH_3)_2$–], 1.01–0.92 [d, 6, $(CH_3)_2CH$–].

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 9.17.

Synthesis of 1,1,5,5-Tetramethyl-*s*-hydrindacene (2) and Attempted Synthesis of 1,1,8,8-Tetramethyl-*as*-hydrindacene (3). 1,4-Bis(3-methyl-3-butenyl)benzene (**13**) was prepared[3d] from 1,4-bis(chloromethyl)benzene and methallylmagnesium chloride. Distillation of the product gave 20% yield of **13**: bp 85 °C (0.1 mm); mass spectrum (70 eV) *m/e* (rel intensity) 214 (M^+, 5), 159 (100), 104 (30), 91 (20), 55 (32), 29 (19); ^1H NMR (neat) δ 6.97 (s, 4, ArH), 4.71 (s, 4, vinyl), 2.82–2.54 (m, 4, $ArCH_2$), 2.38–2.08 (m, 4, $ArCH_2CH_2$), 1.67 (s, 6, $CH_3C(=CH_2)$–].

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.43; H, 10.50.

The diene **13** (1 g) was cyclized by heating at reflux temperature in 50 mL of cyclohexane containing 1 g of Amberlyst-15. The product was recrystallized and shown by GC, NMR, and melting point of an admixture to be identical with **2** from the cyclialkylation of benzene.

Synthesis of 3,3,6,6-Tetramethyl-*as*-hydrindacene (4). 4-Acetyl-6-*tert*-butyl-1,1-dimethylindan (**14**)[15] was oxidized with NaOBr in dioxane[4b] to the carboxylic acid **15a** in 93% yield: mp 191–192 °C (lit.[4b] 190.5–192 °C); ^1H NMR (CCl_4) δ 11.22 (s, 1, COOH), 7.84, 7.22 (s, 2, ArH), 3.23 (t, 2, $ArCH_2$–), 1.93 (t, 2, $ArCH_2CH_2$–), 1.36 (s, 9, *tert*-butyl), 1.27 [s, 6, $ArC(CH_3)_2$–]. The acid **15a** was de-*tert*-butylated in 92% yield as previously described.[4b] Recrystallization from petroleum ether[13] gave 1,1-dimethylindan-4-carboxylic acid (**15b**): mp 145–146 °C (lit.[4b] 145–147.6 °C); ^1H NMR (CCl_4) δ 12.43 (s, 1, COOH), 7.80 (m, 1, ArH), 7.12 (s, 2, ArH), 3.29 (t, 2, $ArCH_2$–), 1.93 (t, 2, $ArCH_2CH_2$–), 1.26 [s, 6, $ArC(CH_3)_2$–].

A sample of **15b** was esterified with ethanol: mass spectrum (70 eV) *m/e* (rel intensity) 218 (M^+, 32), 203 (100), 131 (33), 129 (30), 128 (29), 15 (29); ^1H NMR δ 7.67 (center of m, 1, ArH), 7.12 (s, 1, ArH), 7.07 (center of m, 1, ArH), 4.23 (q, 2, CH_3CH_2–), 3.20 (t, 2, $ArCH_2$–), 1.88 (t, 2, $ArCH_2CH_2$–), 1.35 (t, 3, CH_3CH_2–), 1.22 [s, 6, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.34.

This ester gave a single GC peak.[9a]

Into a 5-L flask equipped with stirrer, thermometer, addition funnel, reflux condenser, heating mantle, and nitrogen flush were placed 700 mL of dry benzene and 260 g (1.9 mol) of diisobutylaluminum hydride. The solution was heated to reflux and a solution of 76 g (0.4 mol) of **15b** in 700 mL of benzene was added over 80 min. The product was cooled and poured onto ice, the mixture stirred, and the pH adjusted to ca. 3 with HCl. Ether extraction, drying ($MgSO_4$), and concentration yielded 65 g (93%) of 4-hydroxymethyl-1,1-dimethylindan (**15c**): bp 100–101 °C (0.5 mm); mass spectrum (70 eV) *m/e* (rel intensity) 176 (M^+, 22), 161 (100), 143 (59), 131 (36), 128 (27), 91 (27); ^1H NMR (CCl_4) δ 6.88 (s, 3, ArH), 4.28 (s, 2, $ArCH_2OH$), 3.84 (s, 1, OH), 2.70 (t, 2, $ArCH_2$–), 1.81 (t, 2, $ArCH_2CH_2$–), 1.18 [s, 6, $ArC(CH_3)_2$–].

In a small flask equipped with a sintered-glass bubbling tube and an exit tube was placed 17.9 g (0.1 mol) of **15c** and the contents were heated to 110 °C. Anhydrous HBr was slowly bubbled through the liquid with periodic shaking over 2 h. The reaction mixture was poured into water, stirred, extracted with ether, dried ($MgSO_4$), and concentrated to give 23 g of crude, lachrymatory brown liquid. Distillation yielded 20 g (84%) of colorless 4-bromomethyl-1,1-dimethylindan (**15d**): bp 110–113 °C (0.4 mm); NMR (CCl_4) δ 6.93 (s, 3, ArH), 4.30 (s, 2. $BrCH_2$–), 2.87 (t, 2, $ArCH_2$–), 1.90 [t, 2, $ArCH_2CH_2$–), 1.21 [s, 6, $ArC(CH_3)_2$–].

A flask equipped with addition funnel, mechanical stirrer, condenser, and nitrogen flask was charged with 5.3 g (0.22 mol) of magnesium turnings and 60 mL of ether. To this was added a crystal of iodine followed by 1 mL of redistilled methallyl chloride. While the mixture was cooled with an ice bath, an additional 18 mL (0.16 mol) of methallyl chloride dissolved in 90 mL of dry ether was added over a 1-h period. The gray slush that resulted was stirred at room temperature for 3 h and then brought to reflux. A solution of 19.8 g (0.083 mol) of **15d** dissolved in 60 mL of ether was added during 1 h. Reflux was continued for 4 h. The reaction mixture was cautiously decomposed with saturated NH_4Cl solution. The resulting mixture was extracted with ether, dried ($MgSO_4$), and concentrated to give 16 g of yellow oil. Distillation yielded 6.6 g (38%) of colorless 4-(3-methyl-3-butenyl)-1,1-dimethylindan (**15e**): bp 80 °C (0.2 mm); mass spectrum (70 eV) *m/e* (rel intensity) 214 (M^+, 10), 199 (35), 159 (100), 158 (77), 143 (36), 129 (34), 128 (31); NMR (CCl_4) δ 6.80 (m, 3, ArH), 4.63 (s, 2, vinylic CH_2), 2.89 (t, 2, $ArCH_2$– of ring), 2.82–2.05 (m, 4, $ArCH_2CH_2$– of chain), 1.86 (t, 2, $ArCH_2CH_2$– of ring), 1.73 (s, 3, CH_3–), 1.21 [s, 6, $Ar(CH_3)_2$–].

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.61; H, 10.33.

Cyclization of 2.7 g (0.012 mol) of **15e** as described for **13** gave 2.6 g of crude **4**. Recrystallization from cold methanol yielded 2.1 g (78%): mp 35–36 °C; mass spectrum (70 eV) *m/e* (rel intensity) 214 (M^+, 15), 200 (18), 199 (100), 143 (26), 128 (11), 41 (10); ^1H NMR (CCl_4) δ 6.75 (s, 2, ArH), 2.72 (t, 4, $ArCH_2$–), 1.89 (t, 4, $ArCH_2CH_2$–), 1.22 [s, 12, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.40; H, 10.51.

Synthesis of 1,1,6,6-Tetramethyl-*as*-hydrindacene (5) and 1,1,7,7-Tetramethyl-*s*-hydrindacene (6). 1,3-Bis(3-methyl-3-

butenyl)benzene (**16**) was prepared[4d] from 1,3-bis(chloromethyl)-benzene and methallylmagnesium chloride. Distillation of the product gave a 80% yield of **16**: bp 95–99 °C (0.2 mm); ^{1}H NMR (CCl_4) δ 7.17–6.73 (m, 4, ArH), 4.70 (s, 4, vinylic CH_2), 2.82–2.52 (m, 4, $ArCH_2$–), 2.33–2.05 (m, 4, $ArCH_2CH_2$–), 1.67 (s, 6, CH_3–).

Cyclization was accomplished by adding 29 g of **16** to 120 mL of refluxing cyclohexane containing 5 g of dried A-15. Reflux was continued for 30 min and the mixture filtered and concentrated to give 28.3 g of **5** and **6** as a 1:1 mixture. Distillation[11] effected separation of **5** from **6**. An early fraction collected at 42 °C (0.3 mm) was identical in NMR spectrum with **6** obtained from the cyclialkylation reaction. This fraction crystallized upon cooling. A late fraction containing **5** did not crystallize: bp 66 °C (0.3 mm) (lit.[4d] 100–105 °C, 0.5 mm); ^{1}H NMR (CCl_4) δ 6.74 (s, 2, ArH), 2.75 (t, 4, $ArCH_2$–), 1.84 (t, 4, $ArCH_2CH_2$–), 1.27 [s, 6, $ArC(CH_3)_2$–], 1.20 [s, 6, $ArC(CH_3)_2$–].

Synthesis of 1,1,4,4,7,7-Hexamethyltrindan (8). The tribromide **17** was prepared from trimethyl 1,3,5-benzenetricarboxylate using a previously described procedure.[16] The tribromide **17**, mp 99–100 °C (lit.[16] 97–99 °C), NMR (CCl_4) δ 7.22 (s, 3, ArH) and 4.34 (s, 6, $-CH_2$–), was converted to **18** in 18% yield using the procedure for the preparation of **15e**. The 1,3,5-tris(3-methyl-3-butenyl)benzene (**18**) was separated from an accompanying diene by distillation: bp 127 °C (0.2 mm); mass spectrum (70 eV) *m/e* (rel intensity) 282 (M^+, 16), 227 (94), 226 (44), 171 (100), 129 (31), 41 (40), 29 (39); ^{1}H NMR (CCl_4) δ 6.67 (s, 3, ArH), 4.63 (s, 6, vinylic CH_2), 2.78–2.05 (m, 12, $ArCH_2CH_2$–), 1.72 (s, 9, CH_3–).

Anal. Calcd for $C_{21}H_{30}$: C, 89.29; H, 10.71. Found: C, 89.37; H, 10.69.

Cyclization of 2.8 g (0.01 mol) of **18** as described for **15e** gave 2.8 g of solid. Recrystallization from petroleum ether[13] yielded 2.0 g (67%) of **8**: mp 238–239 °C; mass spectrum (70 eV) *m/e* (rel intensity) 282 (M^+, 12), 268 (20), 267 (100), 211 (10), 166 (7); ^{1}H NMR (CCl_4) δ 2.82 (t, 6, $ArCH_2$–), 1.82 (t, 6, $ArCH_2CH_2$–), 1.25 [s, 18, $ArC(CH_3)_2$–].

Anal. Calcd for $C_{21}H_{30}$: C, 89.29; H, 10.71. Found: C, 89.10; H, 10.56.

Synthesis of 4-Isopentyl-1,1,5,5-tetramethyl-*s*-hydrindacene (10) from 2. Friedel–Crafts acylation of **2** using 3-methylbutyryl chloride in nitroethane yielded 4-(3-methylbutyryl)-1,1,5,5-tetramethyl-*s*-hydrindacene (**19a**) as a white solid: mp 62–64 °C; mass spectrum (70 eV) *m/e* (rel intensity) 298 (M^+, 21), 283 (61), 242 (19), 241 (100), 57 (19), 41 (19); ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1, ArH), 2.65–2.90 [m, 6, $ArCH_2$– and $ArC(=O)CH_2$–], 2.35 [m, 1, $(CH_3)_2CHCH_2$–], 1.9 (t, 2, $ArCH_2CH_2$–), 1.86 (t, 2, $ArCH_2CH_2$–), 1.23 [s, 6, $ArC(CH_3)_2$–], 1.21 [s, 6, $ArC(CH_3)_2$–], 1.02 [d, 6, $(CH_3)_2CH$–].

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.40; H, 9.92.

Reduction of **19a** using diisobutylaluminum hydride as described above provided the alcohol **19b** in 87% yield: mp 83–86 °C; mass spectrum (70 eV) *m/e* (rel intensity) 300 (M^+, 21), 282 (25), 267 (31), 243 (100), 187 (12), 143 (11); ^{1}H NMR ($CDCl_3$) δ 6.82 (s, 1, Ar), 5.25 (d, of d, 1, $ArCHOHCH_2$–), 3.10 (t, 1, $ArCH_2CH_2$–), 3.02 (t, 1, $ArCH_2CH_2$–), 2.75 (t, 2, $ArCH_2CH_2$–), 2.06 [m, 2, $(CH_3)_2CHCH_2CHOH$–], 1.86 (t, 4, $ArCH_2CH_2$–), 1.63 (s, 1, ROH), 1.38 [s, 3, $ArC(CH_3)_2$–], 1.36 [m, 1, $(CH_3)_2CHCH_2$–], 1.34 [s, 3, $ArC(CH_3)(CH_3)$–], 1.19 [s, 6, $ArC(CH_3)(CH_3)$–], 0.99 (d, 3, CH_3CHCH_3–), 0.97 (d, 3, CH_3CHCH_3–).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.81; H, 10.90.

Amberlyst-15[10] in boiling benzene was used in the dehydration of **19b**. The reaction was indicated by GC to be complete after 10 min. The mixture containing **19c** was isolated and hydrogenated at atmospheric pressure in 95% ethanol using 5% Pd/C catalyst. Filtration, extraction, and distillation provided pure **10**: mp 65–67 °C; mass spectrum (70 eV) *m/e* (rel intensity) 284 (M^+, 12), 269 (100), 211 (40), 197 (52), 183 (36), 165 (40); ^{1}H NMR ($CDCl_3$) δ 6.75 (s, 1, ArH), 2.75 (t, 4, $ArCH_2CH_2$–), 2.5–2.65 (m, 2, $ArCH_2CH_2$–), 1.87 (t, 4, $ArCH_2CH_2$–), ~1.5 [m, 3, $(CH_3)_2CHCH_2CH_2$–], 1.33 [s, 6, $ArC(CH_3)_2$–], 1.18 [s, 6, $ArC(CH_3)_2$–], 0.95 [d, 6, $(CH_3)_2CH$–].

Anal. Calcd for $C_{21}H_{32}$: C, 88.66; H, 11.34. Found: C, 88.79; H, 11.25.

Exhaustive Isoprene Treatment of the Tetramethylhydrindacenes. Procedure C. To a 50-mL, indented, three-neck flask equipped with addition funnel, thermometer, and Teflon-coated magnetic stirring bar was added 0.001 mol of hydrocarbon dissolved in 3.4 g (0.05 mol) of isoprene.[13] The mixture was stirred and cooled to 0 °C. Sulfuric acid (1 g) was added dropwise while the temperature was maintained below 10 °C. The flask contents were poured onto anhydrous Na_2CO_3, diluted with petroleum ether,[13] and analyzed by GC.[9a]

Procedure D. Alternatively, trifluoroacetic acid (TFA) and petroleum ether were used as solvents. For this procedure, based on 0.001 mol of hydrocarbon, 40 mL of TFA, 6 g of sulfuric acid, and 6 mL of petroleum ether[13] were mixed and cooled to 10 °C. A solution of 0.7 g (0.01 mol) of isoprene dissolved in 14 mL of petroleum ether[13] was added with stirring. The temperature was maintained below 20 °C during the addition.

A. 1,1-Dimethylindan (1). The above procedures C and D were applied to **1** in order to obtain products for a comparison with those of the benzene–isoprene cyclialkylation carried out in excess benzene. These processes both gave the same array of cyclialkylation products but more polyisoprene resulted from procedure C.

B. 1,1,5,5-Tetramethylhydrindacene (2). The tetramethylhydrindacene **2** was treated with isoprene (procedure C) but this reaction failed to provide detectable amounts of **7**, **8**, or **10**. However, procedure D gave a product with GC retention time[9a] identical with that of **10**. Procedure D also yielded a diisopentylation product believed to be derived from **10**.

C. 3,3,6,6-Tetramethyl-*as*-hydrindacene (4). Procedures C and D applied to **4** caused low conversion to a product having the same retention time[9a] as the hexamethyltrindan (**7**).

D. 1,1,6,6-Tetramethyl-*as*-hydrindacene (5). Procedure C provided the hexamethyltrindans **7** and **8** in the ratio 1:4.

E. 1,1,7,7-Tetramethyl-*s*-hydrindacene (6). Procedures C and D caused conversion of **6** to **9**. Procedure D produced the higher yield.

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Registry No.—**1**, 4912-92-9; **2**, 17465-54-2; **4**, 61813-30-7; **6**, 6047-64-9; **7**, 55682-87-6; **7** monoketone, 61813-31-8; **8**, 40650-56-4; **9**, 40650-58-6; **9** monoketone, 55712-64-6; **9** diketone, 40650-59-7; **10**, 61813-32-9; **13**, 61813-33-0; **14**, 13171-00-1; **15a**, 61813-34-1; **15b**, 55712-38-4; **15b** Et ester, 55591-12-3; **15c**, 55591-09-8; **15d**, 61813-35-2; **15e**, 55030-58-5; **16**, 6047-59-2; **17**, 18226-42-1; **18**, 55124-94-2; **19a**, 61813-36-3; **19b**, 61813-37-4; benzene, 71-43-2; isoprene, 78-79-5; 1,4-bis(chloromethyl)benzene, 623-25-6; methallyl chloride, 563-47-3; 1,3-bis(chloromethyl)benzene, 626-16-4; trimethyl 1,3,5-benzenetricarboxylate, 2672-58-4; 3-methylbutyryl chloride, 108-12-3.

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(7) (a) Preparative GC separations were obtained with a 10 ft × 4 in. column containing 25% Carbowax 20M on 60–70 mesh Gas Pack W; (b) A 10 ft × 0.375 in. column containing 25% Carbowax 20M on 80–100 mesh, acid-washed Gas Pack was used in a F & M Model 700 GC apparatus equipped with dual thermal conductivity detectors; (c) 25 ft × 0.375 in. column containing 10% UC W-98 on 60–80 mesh, acid-washed Gas Pack.

(8) (a) B. S. Friedman and F. L. Morritz, *J. Am. Chem. Soc.*, **78**, 3430 (1956); (b) D. E. Boone, E. J. Eisenbraun, P. W. Flanagan, and R. D. Grigsby, *J. Org. Chem.*, **36**, 2042 (1971).

(9) (a) GC analyses were carried out on a 11 ft × 0.25 in. column of 80–100 mesh Chromosorb G, DMCS-treated and coated with 5% UC W-98, and

a Hewlett-Packard Model 5750 apparatus fitted with dual thermal conductivity and hydrogen flame detectors; (b) 150 ft × 0.02 in. stainless steel capillary column lined with DC-550 oil at 110 °C; (c) 50 ft × 0.02 in. capillary support coated open tubular (SCOT) column lined with Carbowax 20M mounted in a Perkin-Elmer Mark II flame ionization gas chromatograph.

(10) Amberlyst-15 resin and literature describing it were obtained from Rohm and Haas Co. This reagent shows considerable promise in effecting acid-catalyzed conversions.

(11) A Nester/Faust (NFA-100) autoannular spinning band column was used.

(12) W. M. Harms and E. J. Eisenbraun, *Org. Prep. Proced. Int.*, **4**, 67 (1972).

(13) Mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110B high-resolution mass spectrometer operated under low-resolution conditions at 70 eV. NMR spectra were obtained with a Varian Associates HR-60 or HR-100 spectrometer. Peak positions are reported in terms of δ (pPM) downfield from internal standard tetramethylsilane (δ 0). IR spectra were obtained with a Beckman IR-5A spectrometer as films on NaCl plates or as KBr pellets. Melting points were taken in capillary melting point tubes using a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Cyclohexane used in the reactions was "Baker Analyzed" reagent, spectrophotometric quality. The benzene used was Fisher Certified reagent (thiophene free). Phillips pure grade isoprene was used in all cyclialkylation reactions. The sulfuric acid used was reagent grade. The petroleum ether, bp 60–68 °C, was redistilled before use.

(14) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).

(15) The ketone **14** (Celestolide) was purchased from International Flavors and Fragrances, New York, N.Y.

(16) W. Reppe and W. J. Schweckendiek, *Justus Liebigs Ann. Chem.* **560**, 104 (1948).

Internal Acid Catalysis in the Formation of Imines from Isobutyraldehyde and Monoprotonated Diamines[1]

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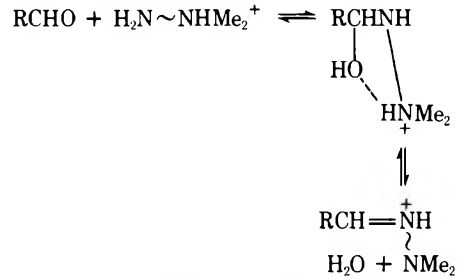
The reactions of isobutyraldehyde with diamines of the type $Me_2N(CH_2)_nNH_2$ where n = 2, 3, 4, and 5 have been studied at various pHs by stopped-flow spectrophotometry. A small amount of aldehyde disappears in an equilibrium process whose rate is too fast to measure. Rough equilibrium constants for this rapid reaction (K_r) are determined in the various runs. The K_r values at various pHs are resolved into K_{Ca}, the equilibrium constant for formation of the carbinolamine i-PrCH(OH)NH$(CH_2)_n$NMe$_2$, and K_{Cah}, the equilibrium constant for formation of the protonated carbinolamine i-PrCH(OH)NH$(CH_2)_n$NHMe$_2^+$. Also determined in the various runs are the equilibrium constants for a slower reaction (K_s), in which equilibrium is not established until about 5–50 s. These are resolved into values of K_{ic}, the equilibrium constants for formation of carbinolamine and imine, and K_{ich}. In all cases K_{ich} covers the formation of protonated carbinolamine and the protonated imine i-PrCH=N$(CH_2)_n$NHMe$_2^+$. However, when monoprotonated 2-dimethylaminoethylamine is the reactant much of the product is probably the 1,1-dimethyl-2-isopropylimidazolidinium ion, and when monoprotonated 3-dimethylaminopropylamine is the reactant an analogous six-membered ring heterocyclic cation is probably formed to a significant extent. Approximate first-order rate constants for dehydration of the carbinolamine mixtures are determined in individual runs. The rate constants obtained at various pHs are resolved into k_{co}, the rate constant for dehydration of the unprotonated carbinolamine, and k_{ch}, the rate constant for dehydration of the protonated carbinolamine. In the case of 2-dimethylaminoethylamine there is also a significant term for catalysis of dehydration of the protonated carbinolamine by the unprotonated diamine. The products $K_{Ca}k_{co}$ and $K_{Cah}k_{ch}$ are reliable second-order rate constants for imination of the aldehyde by the unprotonated and monoprotonated diamine, respectively. The former values give a satisfactory fit to a logarithmic plot against the pK_as of the protonated primary amino groups that includes data on a number of primary monoamines. The values of $K_{Cah}k_{ch}$ for 2-dimethylaminoethylamine and 3-dimethylaminopropylamine are too large by about 7000-fold and 100-fold, respectively, to fit the plot. These deviations are attributed to internal acid catalysis of the dehydration of the intermediate protonated carbinolamine by the dimethylammonio substituent group.

The formation of an imine from an aldehyde or ketone and a primary amine in neutral or basic solution ordinarily involves the reversible formation of a carbinolamine, which, in the rate-controlling step, loses a hydroxide ion to give an iminium ion, whose equilibration with the corresponding imine is established very rapidly.[2,3] This loss of hydroxide ion is uncatalyzed in strongly basic solution but becomes acid catalyzed as the pH is lowered. Nevertheless, increases in the acidity of the reaction solution do not necessarily increase the rate of iminium ion formation, because they decrease the fraction of the amine present in the reactive (unprotonated) form. We thought that relatively rapid iminium ion formation under mild conditions, which is desirable in bifunctional catalysts that are being investigated in this laboratory,[4] could be achieved by internal acid catalysis. We have therefore investigated imine formation from isobutyraldehyde and ω-dimethylaminoalkylamines and learned that with monoprotonated forms of such diamines there may be internal acid catalysis of the dehydration of the intermediate carbinolamine (eq 1). After this work was completed, similar internal acid



(1)

catalysis in iminium ion formation from acetone and various monoprotonated diamines was discovered.[5,6]

Results

Equilibrium Constants for Carbinolamine and Imine Formation. Stopped-flow mixing of aqueous solutions of isobutyraldehyde and amines of the type $Me_2N(CH_2)_nNH_2$ where n = 2, 3, 4, and 5 showed that a small but significant amount of the aldehyde was used up in an equilibrium process that was too fast to measure and that a larger amount of al-

Table I. Equilibrium Constants for Reactions of Isobutyraldehyde with Diamines[a]

Registry no.	Diamine	K_{Ca}, M^{-1}	K_{Cah}, M^{-1}	K_{ic}, M^{-1}	K_{ich}, M^{-1}	K'_{ich}, M^{-1}
108-00-9	$Me_2N(CH_2)_2NH_2$	2.0 (0.3)	5.1 (0.2)	49.7 (0.6)	14.4 (0.4)	38
109-55-7	$Me_2N(CH_2)_3NH_2$	0.9 (0.2)	1.2 (0.2)	103 (9)	20 (7)	67
3529-10-0	$Me_2N(CH_2)_4NH_2$	2.4 (0.2)	0.8 (0.2)	99 (1)	15.6 (0.7)	47
3209-46-9	$Me_2N(CH_2)_5NH_2$	1.8 (0.1)	0.4 (0.1)	100 (2)	24 (2)	114

[a] In water at 35 °C. The parenthesized figures are standard deviations.

dehyde was then used up in a slower equilibrium process. Similar observations had been made earlier in the reactions of isobutyraldehyde with methylamine[7] and other primary amines,[8] and evidence was described that the rapid equilibrium involved addition of the amine to the aldehyde to give carbinolamine and in the slower equilibrium imine is also formed; the equilibrium concentrations of protonated carbinolamine and of iminium ion were too small to detect. In the present case the situation is complicated by the fact that the tertiary–primary diamines (TP) upon protonation may give either a tertiary protonated (HTP^+) or primary protonated (TPH^+) species, as well as a diprotonated form ($HTPH^{2+}$). Furthermore, the carbinolamine formed may exist as an electrically neutral form (Ca) or with the dimethylamino substituent protonated (HCa^+). The equilibrium constant for the rapidly established equilibrium (K_r) may be expressed in terms of total carbinolamine and total diamine as

$$K_r = \frac{[Ca] + [HCa^+]}{[Al]([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}])} \quad (2)$$

in which Al is the free (unhydrated) aldehyde. K_r is an "apparent" equilibrium constant, whose value will be a function of the pH at which it is measured. In determining K_r allowance must be made for hydration of the aldehyde, which occurs to the extent of about 30.6% at equilibrium at 35 °C.[9] Rate constants for establishment of equilibrium between the aldehyde and its hydrate were estimated as described previously.[7,8] For about half the runs, including all those carried out above pH 10.3, more than 2 half-lives for establishment of the dehydration–hydration equilibrium had passed before the first of the transmittance measurements that were extrapolated to zero time to obtain the "initial" transmittance, from which K_r was calculated. In these runs it was assumed that the dehydration–hydration equilibrium was fully established. In most of the other half of the runs, including all those carried out below pH 9.6, the dehydration–hydration equilibrium was estimated to be less than 20% established during the time when the transmittance measurements used for extrapolation were made. In these runs it was assumed that no net aldehyde hydration or hydrate dehydration took place during the establishment of the carbinolamine equilibrium. Five runs on 3-dimethylaminopropylamine were carried out at pH 9.67 where the dehydration–hydration equilibrium was estimated to be about 50% established at the time of the first of the transmittance measurements used in extrapolation. In these runs K_r was calculated by assuming that the dehydration–hydration equilibrium was fully established.

The values of K_r obtained for 2-dimethylaminoethylamine are plotted against the pH in Figure 1. The variation of K_r with pH may be understood in terms of

$$K_r = K_{Ca}f_u + K_{Cah}f_m \quad (3)$$

in which it is written as a function of K_{Ca}, the equilibrium constant for formation of carbinolamine from unprotonated diamine, K_{Cah}, the equilibrium constant for formation of monoprotonated carbinolamine from monoprotonated diamine, f_u, the fraction of diamine that is unprotonated, and

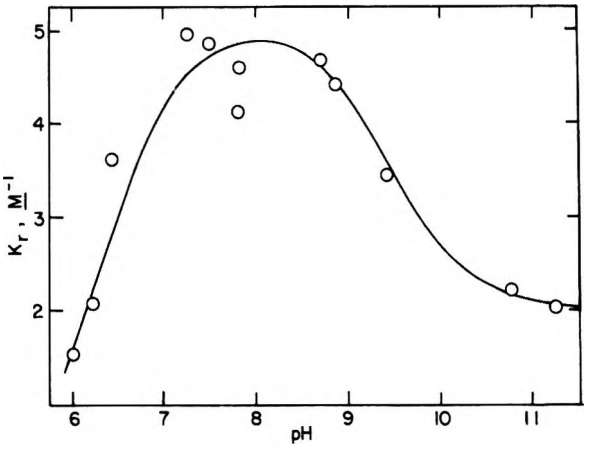


Figure 1. Plot of K_r for isobutyraldehyde and 2-dimethylaminoethylamine in water at 35 °C and ionic strength 0.002–0.43 vs. pH. The line is based on the values of K_{Ca} and K_{Cah} in Table I and an ionic strength of 0.10.

f_m, the fraction of diamine that is monoprotonated (eq 4–7).

$$K_{Ca} = [Ca]/([Al][TP]) \quad (4)$$

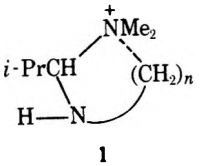
$$K_{Cah} = \frac{[HCa^+]}{[Al]([HTP^+] + [TPH^+])} \quad (5)$$

$$f_u = [TP]/([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}]) \quad (6)$$

$$f_m = ([HTP^+] + [TPH^+])/([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}]) \quad (7)$$

Values of K_{Ca} and K_{Cah} were calculated from eq 3 using the experimentally determined values of K_r and f_u and f_m values calculated from the ionization constants of the diamines.[10,11] The values obtained are listed in Table I, and those for 2-dimethylaminoethylamine were used to draw the line in Figure 1. We suspect that the reliability of these K_{Ca} and K_{Cah} values is considerably poorer than is indicated by the standard deviations shown. This unreliability arises from the rather small differences in absorbances upon which the values are based and upon the uncertainties in extrapolating absorbances to zero time, especially in the case of such rapid reactions as some of those involving 2-dimethylaminoethylamine.

The equilibrium constant for the slower reaction, in which equilibrium is not reached until 5–50 s, is denoted K_s. It covers the formation of both the protonated and unprotonated carbinolamine, an electrically neutral imine (Im), an imine whose tertiary amino substituent is protonated (HIm^+), and possibly a heterocyclic cation (Het^+) of the type **1**. By analogy to earlier



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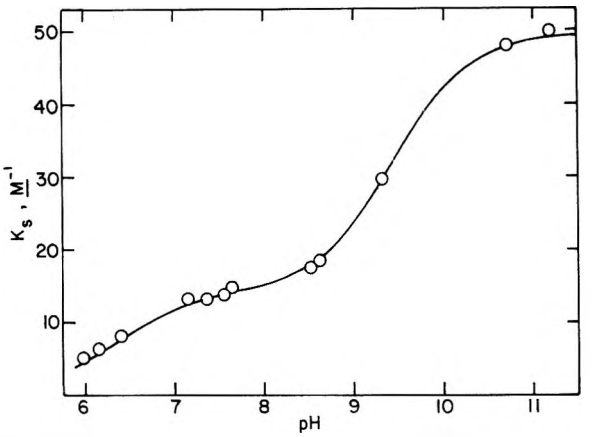


Figure 2. Plot of K_s for isobutyraldehyde and 2-dimethylaminoethylamine in water at 35 °C and ionic strength 0.002–0.43 vs. pH. The line is based on the values of K_{ic} and K_{ich} in Table I and an ionic strength of 0.10.

work[8] we assume that iminium ions will be present in negligible concentrations. Thus the pH-dependent equilibrium constant K_s, defined by

$$K_s = \frac{[Ca] + [HCa^+] + [Im] + [HIm^+] + [Het^+]}{[Al]([TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}])} \quad (8)$$

may be expressed in terms of pH-independent equilibrium constants as shown by

$$K_s = K_{ic}f_u + K_{ich}f_m \quad (9)$$

in which K_{ic}, the equilibrium constant for formation of imine and carbinolamine, and K_{ich}, the equilibrium constant for formation of protonated imine, protonated carbinolamine, and heterocyclic cation, are defined in

$$K_{ic} = ([Im] + [Ca])/([Al][TP]) \quad (10)$$

$$K_{ich} = \frac{[HIm^+] + [HCa^+] + [Het^+]}{[Al]([HTP^+] + [TPH^+])} \quad (11)$$

Values of K_s for 2-dimethylaminoethylamine and 4-dimethylaminobutylamine are plotted against pH in Figures 2 and 3, respectively. The values of K_{ic} and K_{ich} obtained by the method of least squares for all four diamines are listed in Table I. Those for 2-dimethylaminoethylamine and 4-dimethylaminobutylamine were used to draw the lines in Figures 2 and 3, respectively.

Kinetics of the Reactions of Isobutyraldehyde with ω-Dimethylaminoalkylamines. To interpret the reaction kinetics the transformations of carbinolamines to iminium ions have been assumed to be the rate-controlling steps, as appears to be the case with monoamines,[2,3,7,8] and changes in pH during a given run (which exceeded 0.25 only in the case of 3-dimethylaminopropylamine at pH 9.91 ± 0.18, where it was 0.36) were neglected. Within a given run the reaction is treated as a first-order reaction of total carbinolamine (eq 12).

$$\text{carbinolamines} \xrightarrow{k_c} \text{products} \quad (12)$$

Adding the assumption that establishment of equilibrium between the aldehyde and aldehyde hydrate is rapid relative to imine formation we obtain

$$k_c t = \left(\frac{2K_s - 2K_r}{K_s} - \frac{\beta}{\alpha}\right) \ln \frac{K_s\gamma a_0 + \alpha}{K_s\gamma a + \alpha} + \frac{\beta}{\alpha} \ln \frac{a_0}{a} \quad (13)$$

where

$$a = [Al] - [Al]_{eq}$$

$$\alpha = \sqrt{(\delta K_s + \gamma)^2 + 4K_s\gamma[Al]_0}$$

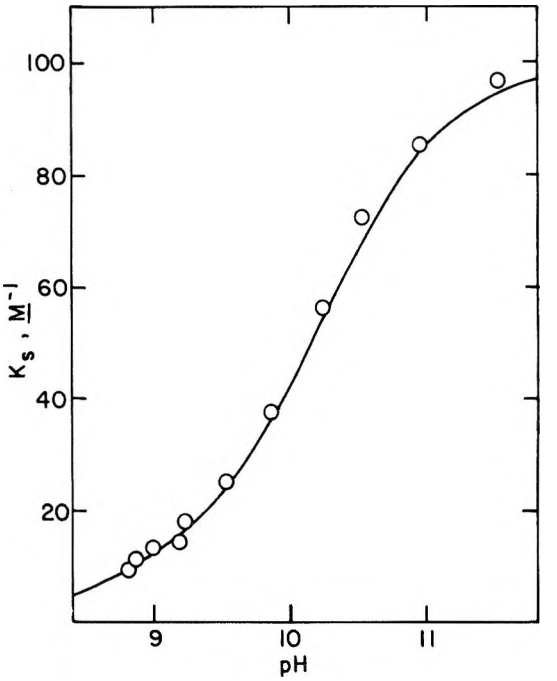


Figure 3. Plot of K_s for isobutyraldehyde and 4-dimethylaminobutylamine in water at 35 °C and ionic strength 0.005–0.15 vs. pH. The line is based on the values of K_{ic} and K_{ich} in Table I and an ionic strength of 0.10.

$$\beta = \frac{K_s - K_r}{K_r}\left(\gamma + \delta K_r + \frac{K_r(\alpha - \delta K_s - \gamma)}{K_s}\right)$$

$$\gamma = 1 + K_h$$

$$K_h = [Ah]/[Al]$$

$$\delta = [TP] + [HTP^+] + [TPH^+] + [HTPH^{2+}] - [Al] - [Ah]$$

which is similar to the rate equation for monoamines.[8] In this equation Ah is the aldehyde hydrate, a_0 is the value of a at time (t) zero, $[Al]_0$ is the initial concentration of aldehyde, and $[Al]_{eq}$ is that at equilibrium. Equation 13 was used in all cases in which the first-order rate constant for approach to equilibrium in hydration was more than five times as large as the rate constant for approach to equilibrium in imine formation (e.g., in all runs made above pH 10). When imine formation was more than five times as fast as hydration, the equation was modified in accordance with the assumption that there was no net hydration of aldehyde or dehydration of aldehyde hydrate during the formation of imine. This modification consists of setting γ equal to 1.0 and setting δ equal to [TP] − [Al]. $[Al]_{eq}$ is set equal to the concentration of aldehyde that would be present if carbinolamine and imine formation were at equilibrium but the concentration of aldehyde hydrate had not changed since the solutions were mixed. When neither hydration nor imine formation could be considered to be fast relative to the other, the rate constant was calculated in each of the two possible ways and the two values (which differed by about 15%, with the rapid-hydration rate constant being larger) were averaged. The values of K_r and K_s used in eq 13 were not those obtained in the given run, but were the values calculated from eq 3 and 9 using the equilibrium constants listed in Table I.

For monoamines the values of k_c obtained at high pH, where the reaction consists of uncatalyzed ionization of the carbinolamine to give hydroxide and iminium ions, were found to be independent of the pH; however, if the amine studied was weakly enough basic to permit measurements to be made in sufficiently acidic solution a hydrogen ion catalyzed reaction became prominent.[8] In the present case the uncatalyzed

Table II. Rate Constants for Dehydration of Carbinolamines Derived from Isobutyraldehyde and Diamines[a]

Diamine	pK_{AmH}[b]	f_t[b]	k_{co}, s^{-1}	k_{ch}, s^{-1}	% std dev of k_c
$Me_2N(CH_2)_2NH_2$[c]	9.30	0.38	3.64 (0.40)	25.2 (1.0)	11
$Me_2N(CH_2)_3NH_2$	9.91	0.30	18.5 (1.3)	41.2 (1.3)	9
$Me_2N(CH_2)_4NH_2$	10.17	0.33	12.8 (0.6)	11.4 (0.5)	8
$Me_2N(CH_2)_5NH_2$	10.44	0.21	20.7 (0.7)	18.5 (0.8)	6

[a] In water at 35 °C. The parenthesized numbers are standard deviations. Unless otherwise stated the values shown were obtained using eq 15. [b] From ref 10. [c] Using eq 16; the k_g value also obtained was 1553 ± 165 M^{-1} s^{-1}.

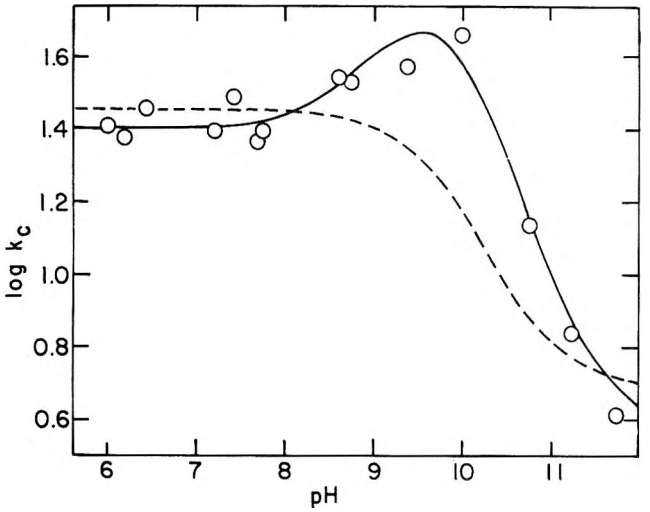


Figure 4. Plot of log k_c for dehydration of carbinolamines vs. pH in the reaction of 2-dimethylaminoethylamine with isobutyraldehyde in water at 35 °C. The dashed line is a fit of the data to eq 15 and the solid line a fit to eq 16 as described in the text.

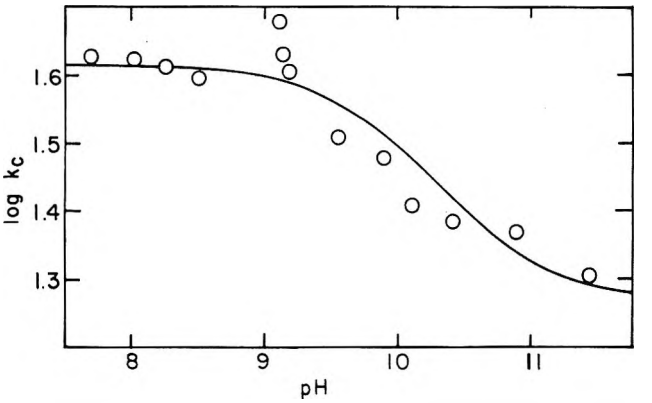


Figure 5. Plot of log k_c for dehydration of carbinolamines vs. pH in the reaction of 3-dimethylaminopropylamine with isobutyraldehyde in water at 35 °C. The line is based on eq 15, the k_{co} and k_{ch} values in Table II, and an ionic strength of 0.10.

reaction would correspond to a first-order reaction of the unprotonated carbinolamine and the hydrogen ion catalyzed reaction would correspond to a first-order reaction of the protonated carbinolamine; that is, k_c would follow

$$k_c = k_{co}f_u' + k_{ch}(1 - f_u') \quad (14)$$

in which k_{co} is the rate constant for the unprotonated carbinolamine, k_{ch} is the rate constant for the protonated carbinolamine, and f_u' is the fraction of the carbinolamine that is unprotonated. Values of f_u' were calculated from

$$f_u' = \frac{K_{Ca}K_{AmH}}{K_{Ca}K_{AmH} + K_{Cah}[H^+]} \quad (15)$$

in which K_{AmH} is the acidity constant of total monoprotonated diamine.

Values of log k_c for the reaction of 2-dimethylaminoethylamine with isobutyraldehyde are plotted against pH in Figure 4. A least-squares fit to eq 14 gave values of k_{co} and k_{ch} of 5.0 ± 1.1 and 28.4 ± 2.7 s^{-1}, respectively, where the ± figures are standard deviations. These values fit the k_c values with a standard deviation of 30%. This fit is illustrated by the dashed line in Figure 4, which was calculated from the given k_{co} and k_{ch} values and an ionic strength of 0.10. Although the experimental measurements were made at ionic strengths ranging from 0.002 to 0.43 (with only the two points below pH 6.4 being at ionic strengths above 0.13), this has no significant effect on how well the dashed line fits the points. The positive deviations seen for the points taken between pH 8 and 11 suggested that there is catalysis of dehydration of the protonated carbinolamine by unprotonated diamine, that is, that k_c should be expressed as shown in

$$k_c = k_{co}f_u' + k_{ch}(1 - f_u') + k_g(1 - f_u')[TP] \quad (16)$$

A least-squares fit of the data to eq 16 gave k_{co}, k_{ch}, and k_g values of 3.64 ± 0.40 s^{-1}, 25.2 ± 1.0 s^{-1}, and 1553 ± 165 M^{-1} s^{-1}, respectively. These values fit the observed k_c values with a standard deviation of 11%. This fit can be illustrated only approximately by a single line in Figure 4, because in eq 16, unlike eq 15, the value of k_c depends on the diamine concentration, and total diamine concentrations ranging from 0.021 to 0.174 M were used in the points shown in the figure. However, the k_g term in eq 16 is almost negligible below pH 7.7, where the free amine concentration was always less than 0.0005 M, and above this pH the total diamine concentration was always between 0.041 and 0.051 M except at pH 9.978, where it was 0.079 M. Hence the solid line in Figure 4 was based on a total diamine concentration of 0.050 M, an ionic strength of 0.10, and the values of k_{co}, k_{ch}, and k_g given. The apparent agreement is not quite as good as the real agreement of eq 16 with the data, which we believe is within the experimental uncertainty.

Application of eq 15 to the data obtained on each of the other three diamines gave k_{co} and k_{ch} values that reproduced the k_c values used with a standard deviation of less than 9%. In each case use of eq 16 gave a negative value for k_g. The data obtained with 3-dimethylaminopropylamine are plotted against the pH in Figure 5; the line shown is based on an ionic strength of 0.10 and the least-squares values of k_{co} and k_{ch} obtained using eq 15. In Table II are the values of k_{co} and k_{ch} obtained for 2-dimethylaminoethylamine using eq 16 and those obtained for the three higher diamines using eq 15.

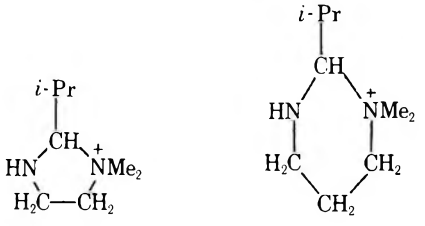
Discussion

The values of K_{Ca} and K_{Cah} we have obtained show no clear trend with the structures of the species involved, although the values obtained with monoamines decreased monotonically with decreasing basicity of the amines.[8] This fact plus the experimental difficulties involved in obtaining the K_{Ca} and K_{Cah} values make us uncertain that the differences among the values are experimentally significant.

Our values of K_{ic} and K_{ich} are much more reliable and show a tendency to decrease with decreasing basicity that is similar to that found previously with monobasic primary amines.[12] In comparing our compounds with the monoamines, however, it should be noted that the linear free energy relationship found with the monoamines related the basicities of the primary amino groups with the equilibrium constants for reaction of the free primary amines with isobutyraldehyde. The pKs of the diamines, however, refer to the basicities of both the primary and tertiary amino groups, and the K_{ich} values in Table I refer to equilibria in which one reactant is a mixture of HTP^+ and TPH^+, depending on whether the primary or tertiary amino group is protonated at the moment. The fractional extents to which the monoprotonated forms of the four diamines are protonated at each of the two possible positions have been estimated by ^1H NMR measurements.[10] Combination of these fractions with the gross acidity constants of the mono- and diprotonated diamines[10,11] gives the microacidity constants, such as K_{HTP}, K_{TPH}, etc. To put them on the same basis as the K_{ic} values and the analogous constants for monoamines,[13] the K_{ich} values were divided by f_t, the fraction of the monoprotonated diamine that is protonated at the tertiary amino group. This gives a constant we shall call K'_{ich}, which has the meaning

$$K'_{ich} = \frac{[HIm^+] + [HCa^+] + [Het^+]}{[Al][HTP^+]} \qquad (17)$$

and the values shown in Table I. The K_{ic} values for primary amines of the type RCH_2NH_2, where R contains an sp^3-hybridized carbon atom by which it is attached to the CH_2 group, are plotted logarithmically against the pK_a values of the protonated amines as solid circles in Figure 6. Our values of K_{ic} are plotted as open circles against the corresponding pK_{TPH} values and our values of K'_{ich} are plotted as triangles against the pK_{HTPH} values (the boldfaced hydrogen in pK_{HTPH} being the one whose acidity is referred to). Although the pK_a values for monoprotonated diamines are independent of the ionic strength, to the degree to which the Davies equation or the limiting form of the Debye-Hückel equation for activity coefficients is reliable, the values of pK_{HTPH} are not; the pK_{HTPH} values plotted are at ionic strength 0.10, a rough average of the ionic strengths at which measurements were made. The line shown in Figure 6 is the least-squares best line (slope 0.26) through the 11 circles. The points for the species of the type $Me_2N(CH_2)_nNH_2$ fall about as near this line as the monoamine points do, except for the case where $n = 3$, but this corresponds to the K_{ic} value whose standard deviation is more than four times as large as that for any other diamine (see Table I). The points for species of the type $Me_2N^+H(CH_2)_nNH_2$ also fall near the line in the cases where $n = 4$ and 5, but the point for $n = 3$ may be too high and that for $n = 2$ is certainly too high. These deviations provide strong evidence that the reaction of monoprotonated 2-dimethylaminoethylamine with isobutyraldehyde gives a cationic product mixture containing a large fraction of the 1,1-dimethyl-2-isopropylimidazolidinium ion **2**. The analogous reaction of 3-dimethylaminopropylamine may produce substantial amounts of **3**. If the deviation of the point for $Me_2N^+HCH_2CH_2NH_2$ from the line in Figure 6 is exactly due to the formation of **2** then the equilibrium constant for formation of **2** is 28 M^{-1}. This is a plausible value, being within an order of magnitude of the value 19 M^{-1} (obtained by multiplying the listed value by $1 + K_h$ to put it on a free-aldehyde basis) for the formation of 1,3-dimethyl-2-isopropylimidazolidinium ions from isobutyraldehyde and monoprotonated *N,N'*-dimethylethylenediamine.[14]



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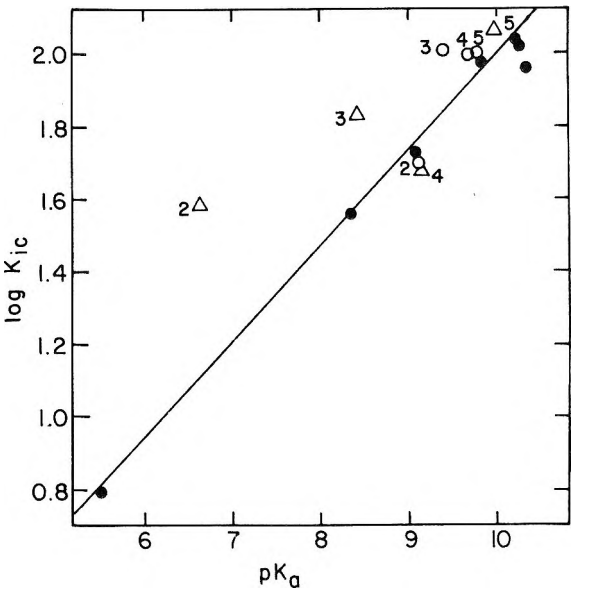


Figure 6. Plot of log K_{ic} vs. pK_a: ●, primary monoamines of the type RCH_2NH_2; ○, diamines of the type $Me_2N(CH_2)_nNH_2$, each point being labeled with the appropriate n; △, protonated diamines of the type $Me_2N^+H(CH_2)_nNH_2$, each point being labeled with the appropriate n.

Table III. Second-Order Rate Constants for Iminium Ion Formation from Isobutyraldehyde and Diamines[a]

Diamine	$K_{Ca}k_{co}$, M^{-1} s^{-1}	$K_{Cah}k_{ch}$, M^{-1} s^{-1}	$K'_{Cah}k_{ch}$, M^{-1} s^{-1}
$Me_2N(CH_2)_2NH_2$	7.36	129	338
$Me_2N(CH_2)_3NH_2$	17.2	47.8	159
$Me_2N(CH_2)_4NH_2$	30.3	8.82	26.7
$Me_2N(CH_2)_5NH_2$	37.7	8.16	38.9

[a] In water at 35 °C.

The values obtained for k_c are markedly dependent on the values of K_{Ca} and K_{Cah} used in the calculations and therefore the large uncertainties in these equilibrium constants lead to large uncertainties in k_c. Our reactions, in which only small concentrations of intermediate carbinolamines are ever formed, approach the case in which the concentration of intermediates is too small to detect. In such a case one could determine the products $K_{Ca}k_{co}$ and $K_{Cah}k_{ch}$ (which would simply be second-order rate constants) without being able to separate the products into their component factors. It is therefore not surprising that when we arbitrarily decreased the values of K_{Ca} and K_{Cah} used in the calculations we obtained values of k_{co} and k_{ch} that had increased to about the same extent, so that the products $K_{Ca}k_{co}$ and $K_{Cah}k_{ch}$ remained almost unchanged. Hence we think that the relative magnitudes of these products for the various amines are more meaningful than are those of any of the increment constants. Thus, as in the case of the monoamines,[8] we shall consider the effect of amine structure on the magnitudes of these products, which are listed in Table III. The $K_{Cah}k_{ch}$ values refer to mixtures of two different forms of the monoprotonated diamine as reactant. They have been divided by f_t to obtain

Table IV. Equilibrium in the Reaction of Isobutyraldehyde with 3-Dimethylaminopropylamine[a]

$[Am]_t$,[b] M	pH		K_r, M^{-1}		K_s, M^{-1}	
	Initial	Final	Obsd	Calcd[c]	Obsd	Calcd[c]
0.0400[d]	11.512	11.360		0.93	64.3	99.7
0.0400	10.924	10.866	0.85	0.95	109	93.4
0.0400	10.514	10.333	0.81	0.98	91.9	78.2
0.0400	10.204	10.012	0.85	1.01	76.0	63.3
0.0400	10.096	9.731	1.22	1.02	60.9	49.7
0.0400	9.672	9.458	1.57	1.07	47.1	38.0
0.0400	9.292	9.086	0.79	1.08	20.4	27.3
0.0400	9.260	9.017	0.88	1.08	21.5	25.8
0.0200	9.239	9.011	1.97	1.08	20.8	26.2
0.0480	8.582	8.458	0.58	0.93	9.81	16.7
0.0560	8.364	8.208	0.53	0.79	7.98	12.9
0.0720	8.093	7.978	0.34	0.61	5.87	9.4
0.104	7.757	7.646	0.24	0.36	3.62	5.1

[a] In water at 35 °C using a total initial aldehyde concentration of 0.0326 M unless otherwise noted. [b] Total initial diamine concentration. [c] From eq 3 or 9 and the equilibrium constants in Table I. [d] Total aldehyde concentration 0.0267 M; 0.0064 M sodium hydroxide added.

Table V. Reaction of Isobutyraldehyde with 4-Dimethylaminobutylamine[a]

$[Am]_t$,[b] M	pH		K_r, M^{-1}		k_c, s^{-1}	
	Initial	Final	Obsd	Calcd[c]	Obsd	Calcd[d]
0.0400[e]	11.524	11.515	2.83	2.29	13.7	12.8
0.0400	11.064	10.950	1.49	2.17	13.6	12.8
0.0400	10.682	10.534	1.85	1.96	12.4	12.6
0.0400	10.344	10.243	2.11	1.66	13.1	12.5
0.0400	9.990	9.864	1.07	1.31	10.8	12.2
0.0440	9.688	9.527	0.92	1.03	10.8	12.0
0.0528	9.362	9.217	1.00	0.76	12.4	11.7
0.0560	9.264	9.176	0.85	0.73	11.0	11.7
0.0640	9.156	8.994	0.52	0.64	11.4	11.6
0.0720	8.990	8.862	0.59	0.52	12.7	11.6
0.0800	8.927	8.806	0.29	0.48	12.8	11.5

[a] In water at 35 °C with an initial total aldehyde concentration of 0.0258 M. [b] Total amine concentration. [c] From eq 3 and the K_{Ca} and K_{Cah} values in Table I. [d] From eq 14 and the k_{co} and k_{ch} values in Table II. [e] 0.0058 M sodium hydroxide added.

$K'_{Cah}k_{ch}$ values, the second-order rate constants for reactions of tertiary-protonated diamines with isobutyraldehyde.

$$K'_{Cah}k_{ch} = K_{Cah}k_{ch}/f_t \quad (18)$$

In Figure 7 the second-order rate constants for iminium ion formation (which is assumed to be the rate-controlling step in the formation of all the products) from isobutyraldehyde and primary amines are plotted logarithmically against the pK_as of the protonated amines. The values for monoamines were published previously.[8] The line (slope 0.87) in the figure is based on these data and on the values for the unprotonated diamines. The unprotonated diamines seem to comprise a slightly more reactive family of compounds than the monoamines, but we are not sure that the difference is large enough to be significant. It is clear, however, that the monoprotonated forms of 2-dimethylaminoethylamine and 3-dimethylaminopropylamine, and perhaps 4-dimethylaminobutylamine, are more reactive than would be expected from the data on the other amines. This increased reactivity—about 7000-fold, 100-fold, and 3.8-fold for the monoprotonated forms of 2-dimethylaminoethylamine, 3-dimethylaminopropylamine, and 4-dimethylaminobutylamine, respectively—is attributed to internal acid catalysis of the dehydration of the intermediate carbinolamine. The stabilities of these transition states of the type 4 appear to decrease monotonically as n increases from 2 to 5. From studies of

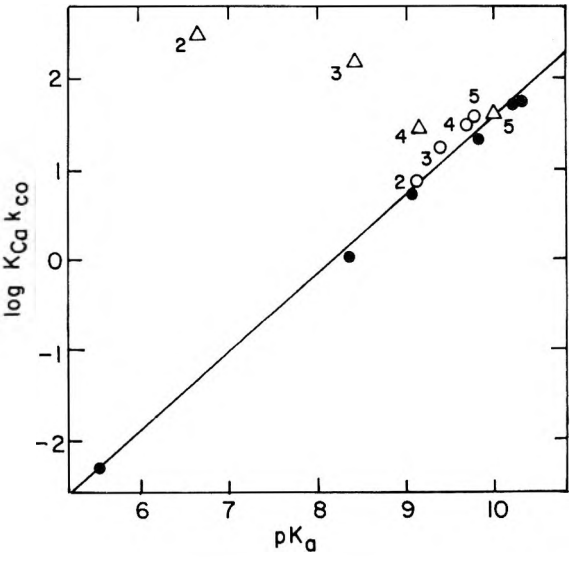
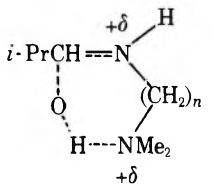


Figure 7. Logarithmic plot of second-order rate constants for iminium ion formation from isobutyraldehyde and primary amines in water at 35 °C vs. the pK_a values of the protonated amines: ●, monoamines of the type RCH_2NH_2; ○, amines of the type $Me_2N(CH_2)_nNH_2$, each point being labeled with the appropriate n; △, amines of the type $Me_2N^+H(CH_2)_nNH_2$, each point being labeled with the appropriate n. The line is the least-squares line through the circles.

Table VI. Reaction of Isobutyraldehyde with 5-Dimethylaminopentylamine[a]

$[Am]_t$,[b] M	pH		K_r, M^{-1}		K_s, M^{-1}		k_c, s^{-1}	
	Initial	Final	Obsd	Calcd[c]	Obsd	Calcd[c]	Obsd	Calcd[d]
0.0400[e]	12.338	12.336	1.73	1.80	100.9	98.9	20.5	20.7
0.0400[f]	11.452	11.408	1.67	1.68	88.5	92.1	21.1	20.7
0.0400	11.004	10.878	1.59	1.49	80.0	77.8	21.6	20.6
0.0400	10.276	10.120	0.92	0.89	39.8	41.6	19.3	20.0
0.0440	9.962	9.802	0.59	0.62	29.6	28.0	19.0	19.6
0.0528	9.643	9.489	0.42	0.40	17.2	17.4	17.4	19.1
0.0640	9.473	9.363	0.12	0.30	11.5	13.6	20.0	19.0
0.0800	9.286	9.155	0.34	0.21	11.8	9.0	20.4	18.8

[a] In water at 35 °C with an initial total aldehyde concentration of 0.0232 M. [b] Total amine concentration. [c] From eq 3 or 9 and the constants in Table I. [d] From eq 14 and the k_{co} and k_{ch} values in Table II. [e] 0.0558 M sodium hydroxide added. [f] 0.0026 M sodium hydroxide added.



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molecular models it appears that the catalysts, which need not have gauche interactions across carbon–carbon bonds in the ground states, have such interactions in numbers that increase as n increases from 2 to 5. There are also varying amounts of eclipsing strains and nonbonded interactions evident from the models.

As we have mentioned, first-order dehydration of the protonated carbinolamine, whose rate we express as $k_{ch}[CaH^+]$, is kinetically equivalent to hydrogen ion catalyzed dehydration of the unprotonated carbinolamine, whose rate may be expressed as $k_h[H^+][Ca]$. For the amines 2,2,2-trifluoroethylamine, 2,2-dimethoxyethylamine, 3-methoxypropylamine, and methylamine k_hK_{Ca} was found to increase monotonically with increasing amine basicity from 2.9×10^7 to 2.7×10^9 M^{-2} s^{-1}. Hence, our amines, whose basicities are in this range, should have k_hK_{Ca} values in this range. It may be shown that our values of $K_{Cah}k_{ch}/(K_{Ca}K_{AmH})$, where K_{AmH} is the gross acidity constant of monoprotonated diamines, are equivalent to k_hK_{Ca}. Thus the values of k_hK_{Ca} for the diamines range from 5.4×10^{10} to 4.3×10^{11} M^{-2} s^{-1} and are much too large to be plausible rate constants for the simple hydrogen ion catalyzed dehydration of unprotonated carbinolamine.

We are not sure why the k_g term in eq 16 is important in the case of 2-dimethylaminoethylamine but not in that of the other diamines. Catalysis of dehydration of monoprotonated carbinolamine by unprotonated diamine is kinetically indistinguishable from catalysis of dehydration of unprotonated carbinolamine by monoprotonated diamine. We have not formulated the reaction in the latter way because no catalysis by external general acids or bases was observed in the formation of imines from primary aliphatic amines and isobutyraldehyde[8] or acetone.[5] However, since it was the values of $K_{Cah}k_{ch}$ that were of principal interest in the present study, we have not carried out the study of additional possible general acid and base catalysts that should be the basis of a detailed discussion of the mechanism of such catalysis.

Experimental and Data Treatment Section

Stopped-flow spectrophotometric measurements were made at the absorption maximum of isobutyraldehyde (285 nm) as described previously; an aqueous solution of the amine and sodium chloride was in one of the syringes of the apparatus and an aqueous solution of the aldehyde and sodium chloride was in the other.[7] The sources and properties of the amines were also described previously.[10] Reaction solutions consisted of given amounts of diamine plus the amount of hydrochloric acid, or, in the case of a few runs at high pH, sodium hydroxide, required to give the desired pH. Final pH values were measured immediately after flushing the reaction solutions from the cuvette. Initial pH values were taken as those obtained when an equal volume of distilled water rather than aqueous isobutyraldehyde was mixed with the amine solution. The pH values were taken as $-\log a_{H^+}$. Activity coefficients of electrically neutral species were taken as 1.0 and those of ions were calculated from the Davies equation,[15] which takes the form

$$\log \gamma = -0.5189Z^2 \left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \qquad (19)$$

at 35 °C, where all the measurements were made.

The absolute uncertainties in K_r and K_s were thought to be relatively independent of the magnitude of K. For this reason, in least-squares treatments of K_r and K_s values it was the sum of the squares of the values of $K_{obsd} - K_{calcd}$ that was minimized. The various rate constants, on the other hand, were thought to be subject to about the same *fractional* uncertainties. Therefore it was the sum of the squares of the fractional deviations, $1 - k_{calcd}/k_{obsd}$, that was minimized. Standard deviations in the resulting parameters were obtained as described by Hamilton.[16]

Data not covered by the figures are listed in Tables IV–VI.

Registry No.—Isobutyraldehyde, 78-84-2.

References and Notes

(1) (a) This investigation was supported in part by Public Health Service Grants AM 10378 from the National Institute of Arthritis and Metabolic Diseases and GM 18593 from the National Institute of General Medical Sciences; (b) Abstracted in part from the Ph.D. Dissertation of F. A. Via, The Ohio State University, 1970.
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The Second Ionization Constant of Hexafluoroacetone Hydrate and the Stability of Species of the Type $R_2C(O^-)_2$[1]

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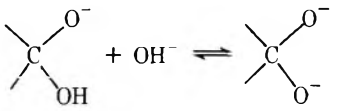
The thermodynamic pK_1 and pK_2 values for hexafluoroacetone hydrate (1,1,1,3,3,3-hexafluoro-2,2-propanediol) in water at 25 °C have been found to be 6.76 and 13.53, respectively. It is estimated that 5.63 of this 6.77 change in pK values arises from the substituent effect of the negative charge two carbons away from the acidic hydroxyl group in the monoanion [$HOC(CF_3)_2O^-$], 0.54 from internal hydrogen bonding in the monoanion, and 0.60 from a statistical effect.

There are many reactions, including the Cannizzaro reaction,[2] the basic hydrolysis of amides,[3] the rearrangements of glyoxal[4] and phenylglyoxal[5] in base to give salts of α-hydroxy acids, and the alkaline cleavage of chloral hydrate,[6,7] β-diketones,[8] ketonylpyridinium ions,[9] β-keto sulfones,[10] 2,6-dihalobenzaldehydes,[11] and phenylpropargyl aldehyde,[12] among others, that have been found to proceed via intermediates having a carbon atom to which two $-O^-$ groups are attached. In order to interpret more fully the kinetic data obtained in such reactions it would be desirable to have a value for the equilibrium constant for the formation of such a species from the monoanion, which is also an intermediate in all the reactions referred to. The equilibrium constant for such a reaction (eq 1) is a function of the second ionization of a *gem*-diol. A



(1)

number of first ionization constants of *gem*-diols have been determined and a Taft equation correlation has been made for a set of eight values.[12] If the substituent effect of an α-O^- substituent could be determined in any specific case it could be used in estimating the second ionization constants. Inasmuch as the second ionization constant is expected to be much smaller than the first, it should be most easily determined in the case of the most acidic *gem*-diol. The most acidic *gem*-diol we are aware of is hexafluoroacetone hydrate (1,1,1,3,3,3-hexafluoro-2,2-propanediol), whose pK_1 has been found to be 6.58 in water at 25 °C.[13] We have therefore determined pK_2 for this compound.

Results

The second ionization constant of hexafluoroacetone hydrate was determined by potentiometric titration in a manner similar to that used previously for the first ionization constant of phenylglyoxal hydrate,[5] except for modifications because of differences in the charge types of the species involved. The titrations were carried out in pairs. One solution contained hexafluoroacetone hydrate; the second was a "matching" solution used, in essence, to calibrate the readings on the pH meter. The first solution was titrated with standard sodium hydroxide to the first end point and then an equivalent amount of additional sodium hydroxide was added, with the pH being read when 0.1, 0.2, 0.3, etc., of it had been added. During the titration the ionic strength is continuously increasing. It was not practical to have the ionic strength of the matching solution increase during the titration in exactly the same way that the ionic strength of the ketone hydrate solution did, but the matching solution was made up so that its ionic strength was essentially equal to that of the ketone hydrate solution at one of the points at which the pH was measured. It was considered that the titration started when the first equivalence point had been reached, that is, that a solution of the monosodium salt of hexafluoroacetone hydrate was being titrated. The matching solution had essentially the same volume and contained a model salt or salts. The same volumes of the same sodium hydroxide solution as was used to titrate the ketone hydrate were added and the pHs read. In one set of titrations the model salt was sodium acetate, whose anion, like the anions derived from the ketone hydrate, has two oxygen atoms attached to the same carbon atom. In another set the model salt was sodium fluoride, whose anion has the full negative charge localized essentially on one atom, like the monoanion of hexafluoroacetone hydrate. In the third set of titrations the matching solutions contained mixtures of sodium fluoride and sodium sulfate so that they contained mixtures of monoanions and dianions, just as the ketone hydrate solutions do during the addition of the second equivalent of base.

If hexafluoroacetone hydrate is abbreviated as H_2Fa the equilibrium constant we are seeking, K_h, is defined in

$$K_h = a_{Fa}/(a_{HFa}a_{OH}) \tag{2}$$

Using the Davies equation,[14] which has the form of

$$\log \gamma = -0.509\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \tag{3}$$

for a unicharged ion at 25 °C, and making the usual assumption that the logarithm of an ionic activity coefficient is proportional to the square of the charge on the ion, permits us to express K_h in terms of concentrations and activity coefficients as shown in

$$K_h = \frac{[Fa^{2-}]\gamma^2}{[HFa^-][OH^-]} \tag{4}$$

in which γ is the activity coefficient of a unicharged ion. From the fact that the autoprotolysis constant of water must be the same in both solutions and the assumption that the observed pH is equal to $-\log a_{H^+}$, we obtain

$$[OH^-] = (\gamma_m/\gamma)[OH^-]_m 10^{pH-pH_m} \tag{5}$$

in which the subscript m's refer to the properties of the matching solution at the same point in the titration. The properties of the matching solution are known, as is the pH of the ketone hydrate solution. The concentration of the dianion is that shown in eq 6, and that of the monoanion in eq 7

$$[Fa^{2-}] = [OH^-]_m - [OH^-] \tag{6}$$

$$[HFa^-] = [H_2Fa]_t - [Fa^{2-}] \tag{7}$$

in which $[H_2Fa]_t$ is the total concentration of H_2Fa in all forms. Substitution of eq 5, 6, and 7 into eq 4 leaves K_h as the only unknown. The result may be rearranged to give eq 8, a quadratic in a, the activity of hydrogen ions in the H_2Fa so-

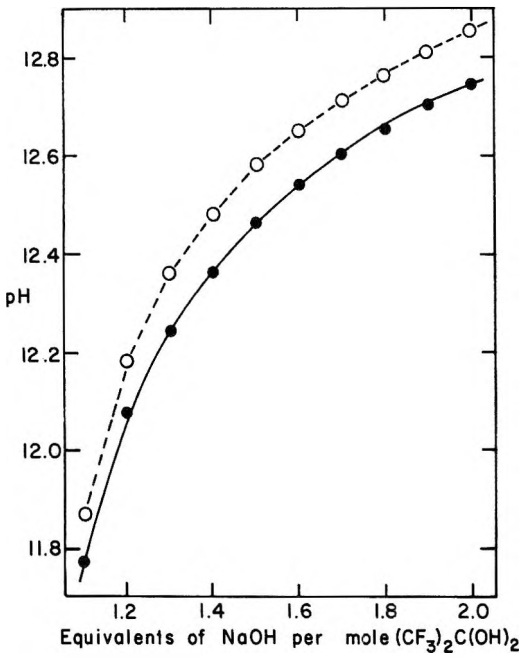


Figure 1. Titration of hexafluoroacetone hydrate with sodium hydroxide: ●, pH of the hexafluoroacetone hydrate solution; ○, pH of the matching solution.

lution. Solution for a permits a nonlinear least-squares treatment[15] of the data on all ten points in a given titration to obtain the best value of K_h.

$$\gamma^4 a^2/(a_m\gamma_m) + \gamma[K_h([OH^-]_m - [H_2Fa]_t) - \gamma^2]a - K\gamma_m a_m[OH^-]_m = 0 \quad (8)$$

Inasmuch as the uncertainties in pH were thought to be more nearly constant than the uncertainties in a, it was the sum of the squares of the fractional deviations in a, that is, $\Sigma(1 - a_{calcd}/a_{obsd})^2$, that was minimized.

The data for the case in which 0.07 M sodium acetate was used are plotted in Figure 1. The pH values obtained in the hexafluoroacetone hydrate solutions are shown as solid circles and those for the matching solution as open circles. The dashed line simply connects the open circles, but the solid line connects the pH's that may be calculated from the open circles and the least-squares best value of K_h, which is listed in the first line of Table I. From the results summarized in Table I we conclude that pK_2 for hexafluoroacetone hydrate is 13.53 ± 0.03.

We considered the possibility that during our titrations with base the hexafluoroacetone hydrate was undergoing a cleavage reaction of the type known to occur with chloral hydrate. This cleavage would replace the monoanions formed from the ketone hydrate by the much less basic trifluoroacetate ions. We therefore titrated 0.07 M ketone hydrate with 2 M sodium hydroxide until more than 2 equiv of base had been added. After the solution had stood at 25 °C for 20 min we back-titrated with 2 M hydrochloric acid and obtained essentially the reverse of the curve that we had obtained in the forward titration. This (and the fact that no gas was evolved) shows that no significant amount of decomposition of the ketone hydrate takes place during the titration.

From the pH (6.68) at the half-equivalence point and the Davies equation we calculate a thermodynamic pK_1 of 6.76 for the ketone hydrate. This is slightly higher than the previously reported value of 6.58,[13] but it is not clear at what ionic strength the literature value was determined or whether it is a thermodynamic ionization constant or not.

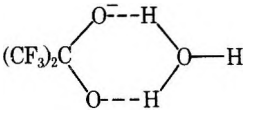
Table I. Acidity of Hexafluoroacetone Hydrate in Water at 25 °C[a]

NaX	[NaX],[b] M	$[Na_2SO_4]$,[b] M	K_h[c]	pK_2
NaOAc	0.0700	0	2.74 (0.05)	13.56
NaOAc	0.0800	0	3.13 (0.03)	13.50
NaF	0.0764	0	2.95 (0.04)	13.53
NaF	0.0764	0	2.85 (0.04)	13.55
NaF	0.0600	0.0100	2.90 (0.06)	13.54
NaF	0.0600	0.0200	2.99 (0.05)	13.52

[a] In all cases the initial total concentration of ketone hydrate was 0.076 ± 0.004 M and that of the sodium hydroxide titrating solution was 2.03 ± 0.05 M. [b] Initial concentration. [c] The parenthesized figures are estimated standard deviations.[15]

Discussion

There is a difference of 6.77 between the pK_1 and pK_2 values we have obtained for hexafluoroacetone hydrate. Of this, 0.60 is a statistical effect, leaving 6.17 as the difference in substituent effects between the α-OH and α-O^- substituents. This is rather larger than the value 4.4 estimated for the ΔpK produced by a charge two atoms away from the acidic hydroxy group using the method of Branch and Calvin.[16] However, the method of Branch and Calvin gives a pK_a of 10.8 for $HOCH_2NMe_3^+$, whose pK_a is actually 9.33.[17] If Branch and Calvin's charge effect had been 5.87 instead of 4.4 their method of estimation of pK_a values would have given the right answer for $HOCH_2NMe_3^+$. A Taft-equation correlation used previously to estimate the acidities of certain α-amino alcohols[18] gives a pK of 14.89 for the hydroxylic proton in $HOCH_2NMe_2$; this leaves 5.56 as the effect of the positive charge in $HOCH_2NMe_3^+$ (neglecting the effect of the extra methyl group). Some of these estimates of the effect of a charge two atoms away from the acidic hydroxy group are almost as large as the ΔpK effect of 6.17 we observe for hexafluoroacetone hydrate, but the differences are all in the direction that would be expected if the monoanion $HOC(CF_3)_2O^-$ were stabilized by internal hydrogen bonding, as Middleton and Lindsey have suggested.[13] Such stabilization of the monoanion can have no effect on the product K_1K_2, which is the equilibrium constant for dissociation of the ketone hydrate to give two protons and the dianion. Hence if the α-hydroxy substituent stabilizes the $-O^-$ by hydrogen bonding, either directly or via intervening water molecules (as in 1), this will increase K_1 and decrease K_2. Therefore $pK_2 - pK_1$



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measures not only the destabilization of the new $-O^-$ group that is formed by the one already present but also the destabilization resulting from loss of the internal hydrogen bond. Middleton and Lindsey's principal argument for the internal hydrogen bond is the fact that the statistically corrected ΔpK_1 produced on replacing the α-hydrogen atom of 1,1,1,3,3,3-hexafluoro-2-propanol by a hydroxy group to get hexafluoroacetone hydrate is 2.42 (2.14, using our pK_1 value), whereas the statistically corrected pK_1 observed for replacing the α-hydrogen atom of phenyltrifluoromethylcarbinols by a hydroxy group is about 1.6. Decreases of about 1.6 in the statistically corrected pK are also noted in the replacement of α hydrogen by hydroxy in methanol,[19,20] 2,2,2-trichloroethanol,[19,20] and 2,2,2-trifluoroethanol.[19,21] The extent of stabilization resulting from internal hydrogen bonding would be expected to increase with increasing acidity of the hydroxylic

proton. The fact that no more such stabilization seems to be occurring in $Cl_3CCH(OH)O^-$ or $F_3CCH(OH)O^-$ than in $HOCH_2O^-$ suggests that in none of the three cases does the internal hydroxy group compete significantly with hydrogen bonding by the more acidic protons of water. The more acidic proton in $HOC(CF_3)_2O^-$ can compete, however, and the result is a ~0.54 larger increase in pK produced on replacing α hydrogen by α-hydroxy. If this interpretation is correct, the negative charge in $HOC(CF_3)_2O^-$ is increasing the pK by 6.17 − 0.54 or 5.63 units. Thus, we would estimate that phenylglyoxal hydrate, for example, whose pK_1 is 11.19,[18] has a pK_2 of 17.42.

Experimental Section

Hexafluoroacetone hydrate (PCR) was used without further purification. The strengths of its aqueous solutions were determined by titration with standard base. Potentiometric titrations were carried out using a Radiometer automatic titrator (ABU 1, PHM 26, and SBR 2c with a type B electrode) with a 2.5-mL buret in the manual mode. The total elapsed time for a titration was less than 15 min and the temperature of the solution was 25.0 ± 0.2 °C.

Registry No.—Hexafluoroacetone hydrate, 677-71-4.

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Chemistry of Trifluoroacetic Anhydride–Haloacetic Acid Reactions with Medroxyprogesterone

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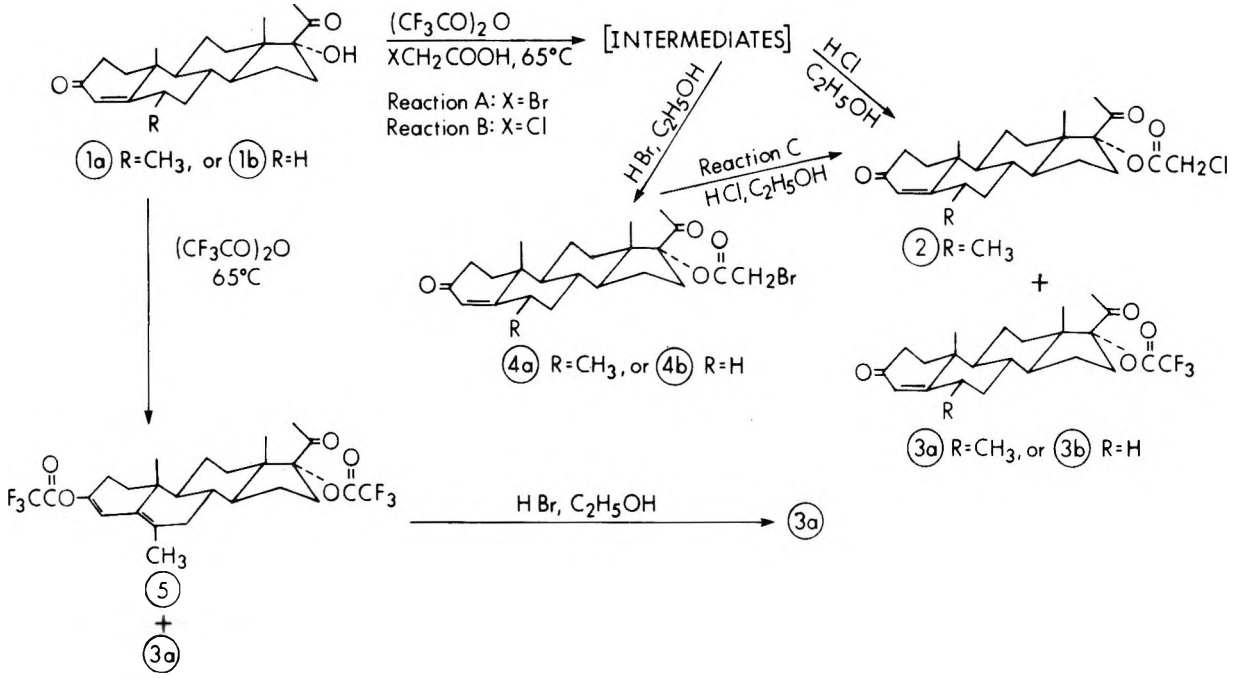
Reaction of medroxyprogesterone with bromoacetic acid–trifluoroacetic anhydride at 25 °C for 1 h gives, after workup, complete recovery of starting material. The same reaction conducted at 65 °C for 1 h produces an inseparable mixture of products. Treatment of the mixture with dilute ethanolic HCl permits isolation of medroxyprogesterone 17-trifluoroacetate and the transhalogenated product medroxyprogesterone 17-chloroacetate, in approximately equal amounts. Substituting ethanolic HBr during the second reaction step provides medroxyprogesterone 17-bromoacetate in 25–30% overall yield. Similar results were obtained with 17α-hydroxy-4-pregnene-3,20-dione. When phenylacetic acid is substituted for bromoacetic acid in the reaction sequence analogous results are obtained. Reaction of medroxyprogesterone at 65 °C in trifluoroacetic anhydride alone gives two products shown to be medroxyprogesterone 17-trifluoroacetate and 3,17α-dihydroxy-6α-methyl-3,5-pregnadien-20-one bis(trifluoroacetate). Electron-withdrawing substitutents on acetic acid appear to direct the mixed anhydride reaction, and this effect is discussed. Both medroxyprogesterone 17-bromoacetate and 17α-bromoacetoxyprogesterone inactivate the enzyme 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans* in a time-dependent and irreversible manner while the corresponding chloroacetoxy and trifluoroacetoxy esters do not.

A series of bromoacetoxyprogesterone isomers was previously synthesized in this laboratory to serve as active site directed irreversible inhibitors to study the active site topography of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans*.[1] Among these alkylating agents, 16α-bromoacetoxy-4-pregnene-3,20-dione, 11α-bromoacetoxy-4-pregnene-3,20-dione, and 17β-bromoacetoxy-4-estren-3-one terminate pregnancy in rats.[2,3] Continuation of these enzymological and reproductive biological investigations required the synthesis of 17α-bromoacetoxyprogesterone (17α-bromoacetoxy-4-pregnene-3,20-dione) and medroxyprogesterone bromoacetate (17α-bromoacetoxy-6α-methyl-4-pregnene-3,20-dione). The latter compound is a steroid alkylating agent structurally analogous to medroxyprogesterone acetate, a powerful progestin.[4] The present report describes the result obtained when the tertiary hydroxyl steroid precursors were treated with haloacetic acid–trifluoroacetic anhydride mixtures under a variety of conditions.

Treatment of medroxyprogesterone (**1a**, Scheme I) with a bromoacetic acid–trifluoroacetic anhydride mixture at 25 °C for 1 h gave, after workup, recovery of starting material. Under similar reaction conditions a variety of aliphatic carboxylic acids are reported to give good yields of the corresponding medroxyprogesterone 17-esters.[4] Therefore, the earlier described reaction conditions had to be modified in order to obtain the desired 17-halo acetates.

When we conducted the mixed anhydride reaction at 65 °C, TLC analysis of the crude product revealed that at least four new compounds had been formed, and 30–40% of the starting material remained unreacted. This mixture could not be separated by either TLC or column chromatography. Since it was likely that some of the products contained a 3-enol ester function[7] we attempted to simplify the mixture by selectively

Scheme I



removing the C-3 ester groups[16] with dilute ethanolic hydrochloric acid (Scheme I). This reaction succeeded in reducing the mixture to three components which could be separated by short column silica gel chromatography[8] into starting material (ca. 40% recovered), medroxyprogesterone 17-trifluoroacetate (**3a**, Scheme I), and medroxyprogesterone 17-chloroacetate (**2**, Scheme I). Isolation of the chloroacetate is interesting in view of the fact that the first esterification step contained bromoacetic acid. The transhalogenation reaction is discussed below. Elemental analysis, NMR, IR, and UV spectral data supported the structural assignments, represented in Scheme I.

When the above reaction sequence was conducted with chloroacetic acid then compound **2** was obtained. Accordingly, when bromoacetic acid was used during the esterification step and ethanolic HBr was used in the second step then medroxyprogesterone 17-bromoacetate (**4a**, Scheme I) was obtained. Treatment of the bromoacetate **4a** with ethanolic HCl resulted in transhalogenation to give the corresponding chloroacetate **2** accompanied by some ester cleavage which produced starting material **1a**.

That ethanolic HCl treatment of the intermediates obtained from the reaction of **1a** with trifluoroacetic anhydride–bromoacetic acid gave chloroacetate **2** was suprising. No bromoacetate **4a** could be detected. Although we had previously encountered similar transhalogenation when a hydroxy steroid was treated with a mixture of bromoacetic acid–thionyl chloride in *N,N*-dimethylformamide (DMF),[1a] the earlier results could be rationalized in terms of a previously established, solvent-dependent nucleophilic hierarchy, i.e., $Cl^- > Br^-$ in DMF.[9] However, our present observation is not consistent with the general view that protic solvents produce the nucleophilic order $Br^- > Cl^-$.[10] To further examine this point **4a** was treated with ethanolic HCl, which expectedly produced **2**. Admittedly, our transhalogenation could result from a mass effect since the calculated molar ratio of Cl to Br in the reaction **1a**-intermediate + HCl → **2** is approximately 9:1. This would imply that the protic nature of the solvent is not very significant in establishing the order of nucleophilicity under our reaction conditions. It is clear, however, that to obtain **4a** from the intermediates derived from trifluoroacetic anhydride–bromoacetic acid and **1a**, ethanolic HBr rather than HCl must be used during selective deacetylation of the 3-enol esters.

Although earlier reports of the mixed anhydride method did not mention the production of steroid trifluoroacetates,[4-6] under our reaction conditions these were among the major products obtained. When medroxyprogesterone was treated with trifluoroacetic anhydride alone at 65 °C, TLC showed that two new components were formed in approximately equal amounts. One of the components was identified as the 17-trifluoroacetate **3a**. The second component (**5**), which possesses greater mobility than **3a** on TLC, was isolated by column chromatography. The IR spectrum of compound **5** contains bands at 1790 and 1725 cm^{-1}, due respectively to the trifluoroacetate and C-20 keto groups. There were no significant absorptions observed in the 1500 to 1700 cm^{-1} region, which suggested the absence of a conjugated C-3 keto group. This was further confirmed by comparing the NMR spectrum of **5** with that of **3a**. The 3,17-bis(trifluoroacetate) **5** exhibited resonance signals at τ 3.75 and 8.33, assigned to H-4 and the C-6 allylic methyl group, respectively. Moreover, the signal due to the C-19 protons of **3a** observed as a singlet at τ 8.80, is shifted upfield by 0.2 ppm to τ 9.02 in the spectrum of **5**. These results coincide with estimated changes in location of shielding and deshielding regions[11,12] associated with a shift in the π-electron system over C-3, C-4, and C-5.

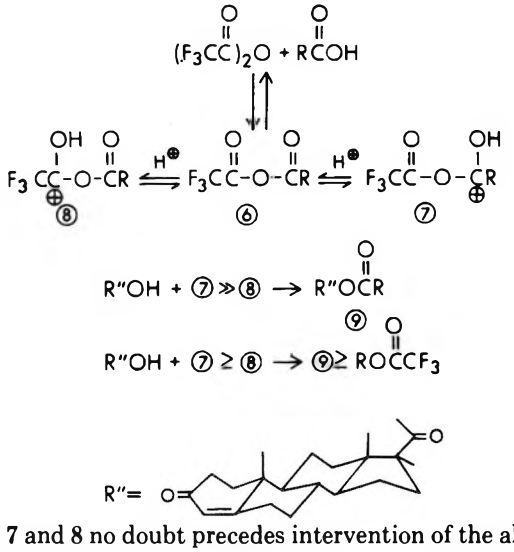
In order to estimate the relative amounts of **3a** and **5** produced in the reaction of **1a** with trifluoroacetic anhydride at 65 °C (Scheme I), just prior to the workup the reaction mixture was chromatographed in varying amounts on TLC plates. The appropriate zones were carefully removed, quantitatively extracted with methanol, and quantitated spectrophotometrically by obtaining the absorbance of the solutions at 235–240 nm. Approximately 20% of **1a** remained unreacted and the products **3a** and **5** comprised 35 and 45%, respectively, of the mixture at this point in the reaction sequence. Apparently during the $NaHCO_3$ workup procedure some of **5** is hydrolyzed to **3a** and **1a**, and a small amount of **3a** is converted to **1a**. This would account for the 40% recovery of starting material and final yields of approximately 30% for each of **3a** and **5** obtained after complete workup. When the reaction mixture is treated with ethanolic HCl and then worked up, about 50–60% of **1a** is recovered along with 40–50% of **3a**.

These results show that during the synthesis of either **2** or **4** a substantial amount of trifluoroacetylation competes against haloacetylation at the 17 position. Moreover, enol esterification at the 3 position can produce several mixed

diesters. Four possible 3,17-diester derivatives and four possible 3- or 17-monoester derivatives are potentially obtainable by reaction of 1 with bromoacetic acid–trifluoroacetic anhydride. Thus, when haloacetic acids are used in the mixed anhydride reaction with 17α-hydroxyprogesterone derivatives it is necessary to selectively convert the 3-enol esters to the corresponding Δ^4 3-ketone with an acid so that the desired 17-monoester derivative can be isolated.

The mixed anhydride reaction, in which trifluoroacetic anhydride is present in large excess while the tertiary hydroxy compound and aliphatic carboxylic acid are in equimolar quantities, generally produces good yields (e.g., 60–90%) of the corresponding tertiary ester, under mild conditions (e.g., 1 h at 25 °C).[13] Therefore, the necessity of using more vigorous conditions to effect only a 30–40% coversion of the tertiary hydroxy steroid to the desired haloacetate in the present synthesis raises questions concerning the limiting factor in the mechanism of this reaction. Most likely the selectivity in condensation of an aliphatic carboxylic acid in the presence of a large excess of trifluoroacetic anhydride with an alcohol to give the corresponding ester is due to the relative ease with which the aliphatic carbonyl group is protonated (7) compared to the trifluoromethylcarbonyl group (8) in the intermediate mixed anhydride (6, Scheme II). Formation of the intermediates 7 and 8 no doubt precedes intervention of the alcohol in the reaction mechanism.[14] Thus the nature of the R group in the anhydride 6 directs this reaction. The presence of a bromine or chlorine atom on the carbon adjacent to the carbonyl group, when a haloacetic acid is used, is expected to have a significant electron-withdrawing effect which destabilizes the corresponding intermediate 7 (R = XCH_2; X = Br or Cl). Thus the amount of intermediate 8 formed relative to 7 when R contains an α-halogen atom is probably sufficient to produce serious competition against the desired esterification process. That electronic effects direct the mixed anhydride reaction is further evidenced by the fact that under the same conditions which produce more than 80% esterification when an aliphatic carboxylic acid is used,[13] phenylacetic acid produces only 15% of the corresponding ester.[15]

Scheme II



The new steroid bromoacetates react with amino acids and form steroid–amino acid conjugates, analogous to those obtained for 11α-bromoacetoxyprogesterone, and under the conditions which we described in elaborate detail elsewhere.[17] Also, incubations of 20β-hydroxy steroid dehydrogenase (4.2×10^{-7} M) with 17-bromoacetoxyprogesterone (5×10^{-5} M) or with medroxyprogesterone bromoacetate in 0.05 M phosphate buffer containing 15% glycerol at pH 7.0 and at 25 °C caused a time-dependent ($t_{1/2}$ = 15 h) and irreversible inactivation, similar to that observed by us with other affinity labeling steroid bromoacetates.[1] By contrast, the corresponding steroid 17-chloroacetates did not inactivate this enzyme. This is consistent with our earlier findings that the more reactive bromoacetoxy group provides a steroid derivative which can be an active *affinity labeling* compound while a chloroacetoxy group does not.[1b]

We are currently conducting experiments with the above affinity labeling steroids to determine the nature of their biological activity in the pregnant rat. Thus far we know that these compounds do not interfere with pregnancy under the same conditions which cause termination of pregnancy when 16α-bromoacetoxyprogesterone is used.[2,3] Therefore the new compounds are being tested for possible long-acting progestational activity, and also for antiovulatory activity.

Experimental Section

All melting points were determined in a Mel-Temp apparatus and are reported uncorrected. Steroids were purchased from Steraloids, Inc., Wilton, N.H., and reagents and solvents were from Fisher Scientific Co. Ultraviolet spectra were determined in methanol with a Beckman Model 25 spectrophotometer. Infrared spectra were determined in KBr, unless otherwise stated, with a Beckman Acculab 4 spectrometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform with tetramethylsilane as internal standard in a Varian T-60 spectrometer, and chemical shifts are reported as τ values. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All the reactions were monitored by thin layer chromatography with Eastman silica gel sheets (no. 6060) containing a fluorescent indicator. Benzene–ethyl acetate (96:4) was used to develop the chromatograms. Iodine and/or ultraviolet light were used for visualization. Silica gel G (Merck AG-Darmstadt) was the adsorbant for short column chromatography. Optical rotations were determined in chloroform using 2% solutions in a 1-dm semimicro (2.5 mL) tube with a Dr. Steeg and Reuter Model SR-5 polarimeter. Removal of solvents was carried out under reduced pressure in a Buchler flash evaporator.

17α-Hydroxy-6α-methyl-4-pregnene-3,20-dione Trifluoroacetate (3a) and 17α-Hydroxy-6α-methyl-4-pregnene-3,20-dione Chloroacetate (2). Reaction A. To a mixture of 300 mg of bromoacetic acid and 1.0 mL of trifluoroacetic anhydride kept at room temperature for 0.5 h was added 700 mg of medroxyprogesterone (**1a**). After stirring the reaction mixture for 1 h at 65 °C, it was cooled, neutralized with 5% $NaHCO_3$, and extracted with ether. The ethereal extract was washed with 5% $NaHCO_3$ and then with water, dried ($MgSO_4$), and filtered. TLC analysis of the filtrate on silica gel G (benzene–ethyl acetate, 96:4) showed it to contain at least four components in addition to starting material. Attempts to separate this mixture by preparative TLC or column chromatography were unsuccessful.

The above ethereal filtrate was concentrated under reduced pressure and the residue was heated under reflux in 25 mL of ethanol containing 0.5% of concentrated HCl for 35 min. The reaction mixture was cooled, neutralized with 5% $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with ether and the extract was washed successively with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and then filtered. The filtrate, which contained three major components, was concentrated to a solid residue and then chromatographed on a short silica gel column eluted with benzene–ethyl acetate (96:4). Pooled fractions gave compounds **3a**, **2**, and starting material **1a**. Recrystallization of **3a** from cyclohexane (trace of acetone) gave 90 mg of crystals: mp 163–165 °C; $[\alpha]^{25}_D$ +117°; λ_{max} 239 nm (ε 16 500). Anal. Calcd for $C_{24}H_{31}F_3O_4$: C, 65.44; H, 7.09; F, 12.94. Found: C, 65.39; H, 7.27; F, 13.32. Strong IR absorptions at 1780 (trifluoroacetate), 1720 (C-20, C=O), 1677 (C-3, C=O), and 1620 cm^{-1} (Δ^4) support structure **3a**. The structural assignment was further confirmed by NMR: τ 9.25 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.90 (s, 3, 21-CH_3), 4.22 (narrow m, 1, 4-CH=).

Compound **2** was recrystallized from petroleum ether–trace of acetone to give 75 mg of colorless needles: mp 200–202 °C; $[\alpha]^{25}_D$ +93°; λ_{max} 239 nm (ε 15 300). Anal. Calcd for $C_{24}H_{33}ClO_4$: C, 68.48; H, 7.90; Cl, 8.42. Found: C, 68.40; H, 8.05; Cl, 8.36. ν_{max} 1730 (ester), 1709 (C-20, C=O), 1669 (C-3, C=O), 1612 cm^{-1} (Δ^4); NMR τ 9.29 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.90 (s, 3, 21-CH_3), 5.93 (s, 2, $ClCH_2CO$), 4.15 (narrow m, 1, 4-CH=).

Reaction B. To a solution of 204 mg of chloroacetic acid in 1.0 mL of trifluoroacetic anhydride kept at room temperature for 25 min was

added 700 mg of **1a**. After working up the mixture as described for reaction A, 50 mg of **3a** and 65 mg of **2** were obtained. These products were identical in all respects (TLC, UV and IR spectra, mixture melting point) with those obtained by reaction A.

Reaction C. Medroxyprogesterone 17-bromoacetate (**4a**, 250 mg) was heated under reflux in 25 mL of ethanol containing 0.5% of concentrated HCl for 35 min. The solution was then worked up as in reaction A. Chromatography was not required since the crude product could be readily crystallized from acetone–petroleum ether to give 190 mg of **2**.

Medroxyprogesterone 17-Bromoacetate (17α-Bromoacetoxy-6α-methyl-4-pregnene-3,20-dione, 4a). Compound **4a** was prepared from **1a** by a procedure similar to that described above for the preparation of compound **2** by reaction A, except that ethanolic HBr was used instead of ethanolic HCl for selective hydrolysis of the intermediates. Chromatography gave compound **4a** which was recrystallized from petroleum ether (trace of acetone) to give 120 mg of colorless needles: mp 172–174 °C; $[\alpha]^{25}_D$ +63°; λ_{max} 239 nm (ε 15 750). Anal. Calcd for $C_{24}H_{33}BrO_4$: C, 61.93; H, 7.15; Br, 17.17. Found: C, 62.10; H, 7.12; Br, 16.95. ν_{max} 1730 (ester), 1720 (C-20, C=O), 1670 (C-3, C=O), 1614 cm^{-1} (Δ^4); NMR τ 9.30 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.93 (s, 3, 21-CH_3), 6.16 (s, 2, $BrCH_2CO$), 4.23 (narrow m, 1, 4-CH=).

17α-Trifluoroacetoxyprogesterone (17α-Hydroxy-4-pregnene-3,20-dione 17-Trifluoroacetate, 3b) and 17α-Bromoacetoxyprogesterone (17α-Bromoacetoxy-4-pregnene-3,20-dione, 4b). Compounds **3b** and **4b** were prepared from **1b** (680 mg) by a procedure similar to that described above for the preparation of compound **4a**. Compound **3b** was recrystallized from acetone–petroleum ether to give 90 mg (10% overall yield) of white crystals: mp 190–192 °C (lit.[5] mp 191–193 °C); $[\alpha]^{25}_D$ +71°; λ_{max} 240 nm (ε 18 000). Similarity of its TLC and IR with that of compound **3a** support the structural assignment which was further confirmed by NMR: τ 9.27 (s, 3, 18-CH_3), 7.90 (s, 3, 21-CH_3), 4.28 (narrow m, 1,4-CH=). Compound **4b** was recrystallized from acetone–petroleum ether to give 110 mg (12% overall yield) of white, crystalline material: mp 165–167 °C; $[\alpha]^{25}_D$ +66°; λ_{max} 239 nm (ε 16 500). Anal. Calcd for $C_{23}H_{31}BrO_4$: C, 61.20; H, 6.92; Br, 17.70. Found: C, 61.40; H, 7.08; Br, 17.60. IR absorption max 1736 (ester), 1717 (C-20, C=O), 1670 (C-3, C=O), 1619 cm^{-1} (Δ^4); NMR τ 9.29 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 7.92 (s, 3, 21-CH_3), 6.15 (s, 2, $BrCH_2CO$), 4.29 (8, narrow m, 4-CH=).

3,17α-Dihydroxy-6-methyl-3,5-pregnadien-20-one Bis(trifluoroacetate) (5). A mixture of 1.4 g of medroxyprogesterone **1a** and 3 mL of trifluoroacetic anhydride was heated under reflux for 1 h at 65 °C under anhydrous conditions. It was then cooled and concentrated to about half of the original volume, stirred for 35 min at room temperature with 350 mL of 5% $NaHCO_3$, extracted with ether, dried, and filtered. TLC analysis of the filtrate showed it to contain three steroidal components in addition to starting material. The filtrate was concentrated to a solid residue and chromatographed on a short silica gel column eluted with benzene–ethyl acetate (96:4). Of the two products isolated from pooled fractions, one was found to be identical in all respects (TLC, mixture melting point, spectroscopic data) with **3a** described above, and the second was further purified by recrystallization from petroleum ether to give 500 mg of **5**: mp 78–81 °C; $[\alpha]^{25}_D$ −100°; λ_{max} 243 nm (ε 7200). Anal. Calcd. for $C_{26}H_{30}F_6O_5$: C, 58.21; H, 5.64; F, 21.25. Found: C, 58.75; H, 6.35; F, 17.1 (the instability of the 3-enol trifluoroacetate group results in the unsatisfactory elemental analysis obtained). ν_{max} 1790 (trifluoroacetate), 1725 cm^{-1} (C-20, C=O); NMR τ 9.27 (s, 3, 18-CH_3), 9.02 (s, 3, 19-CH_3), 8.33 (s, 3, 6α-CH_3), 7.90 (s, 3, 21-CH_3), 3.75 (narrow m, 1, 4-CH=).

Conversion of 5 into 3a. Compound **5** (50 mg) was heated under reflux in 4 mL of 0.5% ethanolic HBr for 30 min. The reaction mixture was cooled, neutralized with 5% $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with ether and the extract was washed successively with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and then filtered. The filtrate was concentrated to a solid residue which was crystallized from cyclohexane (trace of acetone) to give 35 mg of colorless needles, identical (TLC, mixture melting point, spectroscopic data) with **3a**, described above.

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Registry No.—**1a**, 520-85-4; **1b**, 68-96-2; **2**, 61886-08-6; **3a**, 61886-09-7; **3b**, 560-10-1; **4a**, 61886-10-0; **4b**, 61886-11-1; **5**, 61886-12-2; trifluoroacetic anhydride, 407-25-0; bromoacetic acid, 79-08-3; chloroacetic acid, 79-11-8.

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Methyl-Terminated Perfluoroalkyl Iodides and Related Compounds

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1,1-Difluoroethyl iodide (**2**) was prepared from vinylidene fluoride and hydrogen iodide in 96% yield. It telomerized with tetrafluoroethylene with acyl peroxide catalysis, but other radical generators were ineffective. The telomers $CH_3(CF_2)_nI$ (**3**) reacted thermally with ethylene to form $CH_3(CF_2)_nCH_2CH_2I$ (**4**). These in turn were converted to alcohols (**6**), (meth)acrylates (**7**), and chlorosulfates (**8**) by replacement of the iodine atom. The radical $CH_3(CF_2)_n\cdot$, when formed during telomerization of **2** with tetrafluoroethylene or during reaction of **3** with ethylene, may lose CF_2 groups successively, since products derived from $CH_3(CF_2)_{n-y}$ (y = 1, 2, 3) were always identified in the reaction mixtures. The presumed difluoromethylene fragment is held responsible for some of the other trace by-products. $CH_3CH_2CF_2CF_2I$ was prepared from $ICH_2CH_2CF_2CF_2I$.

Polymers derived from 2-perfluoroalkylethyl (meth)acrylates $CF_3(CF_2)_nCH_2CH_2OCOCR{=}CH_2$ (**1**) are useful in treating the surfaces of textiles and other substrates. Since theoretical analysis[1] suggested that similar compounds with a terminal methyl group might exhibit valuable surface properties, the compounds **7** (Chart I) were prepared for evaluation. Telomerization of 1,1-difluoroethyl iodide (**2**) with tetrafluoroethylene (TFE) was employed for synthesis of the intermediates (eq 1).

Chart I

$$CH_2{=}CF_2 + HI \longrightarrow \underset{\mathbf{2}}{CH_3CF_2I} \xrightarrow{C_2F_4} \underset{\mathbf{3}}{CH_3(CF_2)_nI}$$

$$\xrightarrow{C_2H_4} \underset{\mathbf{4}}{CH_3(CF_2)_nCH_2CH_2I} + CH_3(CF_2)_n(CH_2CH_2)_mI \quad m = 2, 3\ldots$$

$$\mathbf{4} + SO_3 + H_2SO_4 \longrightarrow CH_3(CF_2)_nCH_2CH_2OSO_3H$$

$$\underset{\mathbf{5}}{(+\ I_2 + SO_2)}$$

$$\xrightarrow{H_2O} \underset{\mathbf{6}}{CH_3(CF_2)_nCH_2CH_2OH}$$

$$\mathbf{6} + CH_2{=}CRCOOR' \quad R' = CH_3,\ C_2H_5$$

$$\longrightarrow \underset{\mathbf{7},\ R = H,\ CH_3}{CH_3(CF_2)_nCH_2CH_2OCOCR{=}CH_2} \longleftarrow \mathbf{4} + CH_2{=}CRCOOK$$

$$\mathbf{4} + ClSO_3H \longrightarrow \underset{\mathbf{8}}{CH_3(CF_2)_nCH_2CH_2OSO_2Cl} (+\ \mathbf{5}) + HCl$$

$$+ SO_2 + I_2 + H_2SO_4$$

$$\mathbf{4} + \text{base} \longrightarrow \underset{\mathbf{9}}{CH_3(CF_2)_nCH{=}CH_2} \xrightarrow{KMnO_4} \underset{\mathbf{10}}{CH_3(CF_2)_nCOOH}$$

$$CH_3CF_2I + xC_2F_4 \xrightarrow{\text{radical}} CH_3CF_2(CF_2CF_2)_xI \qquad (1)$$

The required telogen **2** had already been prepared by iodine-catalyzed addition of hydrogen iodide to vinylidene fluoride (1,1-difluoroethane); on a small scale, the reaction was slow.[2] Actually, the reaction is very rapid and exothermic as soon as sufficient product has been formed to act as a mutual solvent for vinylidene fluoride and hydrogen iodide. Added iodine may not be really essential; the traces of iodine present in commercial hydrogen iodide are probably quite sufficient, if in fact necessary. The reaction can be conducted as quickly as the available cooling permits. Pure **2** was obtained in 96% yield.

Telomerization. Many literature methods for telomerization of *per*fluoroalkyl iodides with TFE failed with **2**. Perfluorobutyl iodide difluoride ($C_4F_9IF_2$)[3] reacted violently with **2** at room temperature to yield iodine; this mixture did not react with TFE. The ultraviolet light passed by Pyrex glass did not cause telomerizations at temperatures to 80 °C and TFE pressures to 200 psi. Azonitriles such as 1,1′-azobis(cyclohexanecarbonitrile) were ineffective. Di-*tert*-butyl peroxide likewise gave no telomer at temperatures to 135 °C where the peroxide decomposes fairly rapidly to *tert*-butoxy radicals. This peroxide was not tested with **2** at 160 °C where the *tert*-butoxy radical dissociates to methyl radical and acetone; pentafluoroethyl iodide will telomerize with TFE under these conditions, but not at 130 °C. Methyl amyl ketone peroxide at 80 °C failed to initiate telomerization; it is frequently used in other telomerizations with TFE. *tert*-Butyl hydroperoxide with cobaltous ion promoter was initially effective, but the reaction slowed to a halt as insoluble cobaltous iodide precipitated.

Thermal telomerization (no catalyst) occurred at 200 °C, analogous to the thermal telomerization of *per*fluoroalkyl iodides with TFE. However, the vapor pressure of the telogen **2** is nearly equal to the cylinder pressure of TFE, and it was impractical to add TFE continuously to achieve reasonable conversions. On the other hand, when the higher telogen $CH_3CF_2CF_2CF_2I$ had become available (see below), its lower vapor pressure permitted continuous feed to achieve TFE conversions of 0.7 mol/mol of telogen.

Fortunately, *acyl* peroxides are very effective. Benzoyl peroxide was tested first, despite its penchant for undergoing induced decompositions,[4] and telomerization occurred readily. However, the iodobenzene by-product boils too close to the telomer **3**, n = 7, for efficient separation. Other by-products included $C_6H_5CF_2CH_3$ and its isomeric ring-iodinated derivatives, and iodobenzoic acids. Hence other commercially available peroxy acid derivatives were screened. The search culminated with the demonstration that *tert*-butyl peroxypivalate ("Lupersol" 11) was extraordinarily effective, even at 0.04 mol % concentration. It appears that alkoxy radicals RO· are inefficient in abstracting iodine from R_FI, since a high-energy hypoiodite ROI would be the product. On the other hand, carbon radicals R· from decomposition of acyloxy radicals RCOO· or *tert*-butoxy radicals would form RI, and that abstraction should be nearly thermoneutral.

Telomerizations were performed by feeding TFE continuously to the telogen–catalyst mixture at 50 °C, 120–160 psi, at such a rate that the temperature did not rise. In the small apparatus described in the Experimental Section, a cooling coil permitted rapid addition. Usually 0.5 mol of TFE was added per mol of telogen so as to maximize the quantities of the desired telomers n = 5–11. Larger amounts of TFE in-

creased the quantities of higher telomers, $n > 11$. The individual telomers were isolated by fractional distillation.

Curiously, the expected telomers **3** (n = odd integer) were accompanied by small amounts of products with n = an even integer. The TFE used was free of hexafluoropropene; the by-product did not possess a trifluoromethyl group $-CF_2CF(CF_3)-$ (NMR). The only explanation apparent at this writing is that the growing radical $CH_3(CF_2)_n\cdot$ lost the elements of CF_2 (difluoromethylene) to give $CH_3(CF_2)_{n-1}\cdot$. Other trace products found in the crude telomer product may have been derived by insertion of the lost difluoromethylene into C-H bonds (see Experimental Section).

Ethylene Insertion. The pure individual telomers **3** were heated at 195 °C under 200–250 psi ethylene pressure. Only small amounts of ethylene telomers $CH_3(CF_2)_n(CH_2CH_2)_mI$ accompanied the major product **4**. The hydrocarbon radical $RCH_2\cdot$ is much more reactive toward chain transfer with R_FI than is the fluorocarbon radical $R_F\cdot$; hence most ethylene adduct radicals are destroyed by chain transfer before they can add more ethylene. Moreover, a telogen **3** is readily reinitiated, but product **4** is not. Independent experiments showed that neither **4** nor the related $R_FCH_2CH_2I$ reacted significantly with ethylene at 200 °C. See also the attempted telomerizations of TFE with ethyl iodide below.

In these reactions also, a few of the intermediate radicals $CH_3(CF_2)_n\cdot$ lost difluoromethylene groups, since the compounds $CH_3(CF_2)_{n-y}CH_2CH_2I$ (y = 1, 2, 3) were detected by GC/MS. The unreacted **3** also contained lower homologues not present originally. Traces of products derivable from ICF_2CF_2I and ethylene were detected as well (see below).

Hydrolysis of 4 to Alcohols 6. Basic hydrolysis of the iodides **4** causes chiefly elimination to olefins **9** (see following section).[5] Hence **4** were hydrolyzed by oleum and hot 30% sulfuric acids to **6**. Hydrolysis of the chlorosulfates **8** yielded a mixture of products.

Preparation of (Meth)acrylates 7 (see Chart I). Some of the iodides **4** were transformed to esters by heating them with potassium (meth)acrylate in dry *tert*-butyl alcohol. Although the yields were acceptable, the reaction was slow and always gave some of the olefin as by-product. Preferably, alcohols **6** were transesterified with methyl methacrylate or ethyl acrylate, using tetraisopropyl titanate as ester interchange catalyst. Yields by the second procedure were nearly quantitative, and no olefin was formed.

The (meth)acrylates formed by either procedure polymerized readily with conventional initiators in bulk, in solution, or in emulsion.[6]

Preparation of Olefins 9. Some of the olefins were isolated from the potassium methacrylate displacements. Others were prepared by refluxing the iodide **4** with ethanolic potassium hydroxide. Heating **4** with pyridine gave slow and incomplete elimination. One of the olefins (n = 9) was oxidized to the acid **10** with potassium permanganate.

Reaction of Iodides 4 with Chlorosulfonic Acid. When the iodides **4** were heated with chlorosulfonic acid, the chlorosulfates **8** were the major products. Most of the remainder was alkylsulfuric acid **5**, but a small amount of the related chloride $CH_3(CF_2)_nCH_2CH_2Cl$ was also formed. The chlorosulfates were identified by elemental analysis, NMR, and IR.

Curiously, the mass spectra were anomalous. The compounds **8**, n = 3 (or 5), should exhibit a pair of peaks for m/e 308, 310 (or 408, 410) (chlorine isotopes). Yet these peaks were not observed. Rather, the most abundant peak was m/e 303 (or 403), with minor peaks at m/e 304, 305, and 307 (or 404, 405, and 407). Even more curiously, the higher homologue **8**, n = 7, gave the expected peaks at m/e 508, 510 and none of the m/e 503 or other anomalous peaks. No explanation is apparent for these peculiar results.

Synthesis of $CH_3CH_2CF_2CF_2I$ (15). The iodide **15** was sought as the starting point for preparation of similar derivatives. A priori, the most attractive synthesis would be telomerization of ethyl iodide with TFE. Bartlett and Nozaki[4] have shown that benzoyl peroxide undergoes induced decomposition in ethyl iodide, presumably because ethyl radicals are formed. However, ethyl iodide is a much poorer chain-transfer agent than perfluoroethyl iodide or other R_FI; hence one would expect that a growing radical $C_2H_5(CF_2CF_2)_n\cdot$ should more readily add to TFE than transfer with ethyl iodide. Unfortunately, this prediction was borne out. When ethyl iodide containing benzoyl peroxide was heated at 80 °C under 120 psi pressure of TFE, the product was a fine dispersion of polymer in ethyl iodide. Iodobenzene and carbon dioxide were formed, but no GC peaks corresponding to the low telomers were seen. With *tert*-butyl peroxide at 135 °C (half-life 3.86 h), the product was a clear, greenish liquid with a white, fluffy solid. The liquid phase contained only traces of low telomer.

A second route was examined (eq 2). Two experiments

$$CH_3CH{=}CH_2 + CF_2{=}CF_2 \xrightarrow{150\ ^\circ C} CH_3CH(-CH_2)-CF_2-CF_2 \xrightarrow{\text{pyrolysis}} CH_3CH{=}CF_2 + CH_2{=}CF_2$$
$$CH_3CH{=}CF_2 \xrightarrow{HI} CH_3CH_2CF_2I \qquad (2)$$

showed that the first step proceeded in only about 50% yield based on TFE. Since the pyrolysis gives only moderate yields, this route was not further pursued. It is unfortunate that 2-butene fails to undergo cycloaddition with TFE.[7,8]

Finally, the route shown in Chart II was developed with

Chart II

$$C_2F_4 + I_2 \longrightarrow \underset{\mathbf{11}}{ICF_2CF_2I} \xrightarrow{C_2H_4} \underset{\mathbf{12}}{ICH_2CH_2CF_2CF_2I} + ICH_2CH_2CF_2CF_2CH_2CH_2I$$

$$\mathbf{12} + NaBH_4 \longrightarrow \underset{\mathbf{13}}{ICH_2CH_2CF_2CF_2H}$$

$$\mathbf{12} + Et_3N \longrightarrow \underset{\mathbf{14}}{CH_2{=}CHCF_2CF_2I} \xrightarrow{N_2H_2} CH_3CH_2CF_2CF_2I$$

moderate success. Since the diiodide **12** was readily prepared,[9] the problem was reduced to finding a method for selectively hydrodeiodinating CH_2I in the presence of CF_2I. Chromous sulfate–ethanolamine in dimethylformamide[10] furnished only a small amount of low-boiling products, a complex mixture containing only a trace of **15** (GC/MS); most of the **12** was recovered. Sodium borohydride in methanol reduced **12** slowly to **13** in about 65% yield (GC). **13** was identified by NMR and GC/MS. Though potentially a useful method for converting R_FI to R_FH,[11] borohydride reduction could not be employed in the synthesis of **15**. Apparently neither one-electron nor two-electron reducing agents attack R_HI in preference to R_FI.

Heating **12** with excess triethylamine in *tert*-butyl alcohol eliminated hydrogen iodide slowly to form the olefin **14** in about 50% yield.[12] Potassium hydroxide in isopropyl alcohol effected some elimination, but much of material was converted either to water-soluble or gaseous products. The olefin was then reduced to **15** with diimide[13] generated from hydrazine–hydrogen peroxide with cuprous chloride catalysts. Sufficient **15** was obtained to permit identification, but not enough to study its telomerization, etc. This two-step route

from **12**, with more study, could become a satisfactory source of **15**.

Experimental Section

Apparatus. Small-scale experiments under pressure were conducted in graduated heavy-wall Pyrex tubes or bottles (respectively 3 and 6 oz capacity) purchased from the Fischer-Porter Co. under the name "aerosol compatibility tubes". These are closed with metal connectors equipped with replaceable Viton fluoroelastomer O-rings. The basic assembly is pictured in the F-P catalog. The connector for the reaction bottle was drilled to accommodate a cooling coil, a thermocouple well, and a valved sampling tube (dip-leg) fashioned from 0.125 in. Monel tubing; these were welded to that connector. An adapter (0.125 in pipe to 0.25 in. tube) screwed into the connector was attached to a cross. One arm of the cross was connected through a tee to a 30 in.–300 psi gauge and to a ball-valved vent line leading to the top of the hood. The second arm of the cross led through a needle valve to the vacuum manifold. The third arm led to the interconnection described below.

Gases were condensed and measured in a similar tube lacking the dip-leg and cooling coil. It was similarly furnished with a gauge and vent, and attached to the vacuum manifold adjacent to the reaction bottle. The reaction bottle and gas tube were interconnected through the third arms of the crosses to a solenoid-operated valve. A tube led from this interconnection to a Mon-O-Con pressure gauge equipped with adjustable contacts. The output from this gauge opened or closed the solenoid valve as the pressure fell or rose between the upper and lower set points. The solenoid valve was protected by a ball valve between it and the reaction bottle.

The vacuum manifold was 1 in. (i.d.) Monel pipe. A 1-in. ball valve led to a conventional trapped pumping system. Valved ports led to trapped pressure gauges and to connectors for gas cylinders. All permanent connections were assembled by Heliarc welding; temporary connections were made with Swagelok connectors. All but the solenoid valves were Whitey needle or ball valves (0.25 in.). All tubing was 0.25 in., except as noted. Monel metal was used throughout to minimize corrosion.

The cooling coil in the reaction bottle carried laboratory water through a throttling needle valve and a solenoid-operated valve (Hoke). A Simplytrol controller attached to the thermocouple provided the signals to open and close the water valve to maintain an exothermic reaction at constant temperature. The glassware was dried at 200 °C for 24 h before use.

Gaseous reagents were transferred from cylinders through the vacuum manifold and condensed in evacuated tubes at −196 °C, then warmed to −80 °C for measurement. Vinylidene fluoride was used from cylinders as supplied (Matheson). Tetrafluoroethylene was stored outdoors and delivered from the cylinder at 30 psi through a copper line past a mineral oil bubbler and a silica gel tower (to remove the limonene inhibitor) into the vacuum manifold. Uninhibited TFE must never be stored because of the danger of explosive polymerization or disproportionation. The temperature of the condensed gas was then adjusted with an appropriate bath to yield the desired vapor pressure.

In operation, any involatile reagents were placed in the reaction bottle with a magnetic stirrer bar. The bottle was attached to the connector, chilled to a temperature at which the contents had negligible vapor pressure, and evacuated. Note: the cooling coil must not contain water from a previous experiment; it may be conveniently flushed out with methanol and dried with air. Where desirable, liquids were degassed by successive freeze–thaw cycles. The temperature of the reaction bottle was then adjusted with an appropriate bath. For temperatures above about 50 °C, an electric cooking pot with thermostatic control, filled with water or peanut oil, was a very convenient constant-temperature bath. The gaseous reagent was then added through the interconnection at the selected constant pressure.

In over 100 experiments with this apparatus, no bottle breakage or other accidents occurred. However, the experimenter must realize that pressure reactions in glass are hazardous. Care is required to avoid scratching the glass bottles. In all our work, sturdy shields of 0.5 in. Lucite abrasion-resistant sheet guarded all the glass equipment, including the faces of the gauges. A further safety note: the violent and exothermic decomposition of TFE under pressure may be initiated by traces of oxygen; good vacuum-line technique is required at all times.

The apparatus and technique described permitted reactions up to about 90 °C and 200 psi, and could make about 190 mL of total product. For higher temperatures and pressures, 400-mL shaker tubes of Hastelloy C were used in a laboratory specially equipped for high-pressure research. The large preparations of 1,1-difluoroethyl iodide were conducted in a 2-gal stirred autoclave of Hastelloy B equipped with a cooling coil.

1,1-Difluoroethyl Iodide. Several exploratory experiments were conducted in the apparatus described. A little iodine was placed in the bottle, and hydrogen iodide was transferred in from a cylinder (Matheson). A new cylinder contained enough hydrogen or other noncondensible gas to impede the transfer, but it was readily removed by pumping out the manifold several times (liquid nitrogen trap!). The problem did not recur during subsequent uses of that cylinder. Note the narrow liquid range of hydrogen iodide [mp −51 °C, bp −35 °C (760 Torr)]. Alternatively, and more conveniently with larger runs, the cylinder was chilled to about −30 °C and liquid hydrogen iodide was poured from the cylinder through a copper coil into the bottle at −80 °C; the exit side was protected by −80 °C traps. The bottle was then weighed, connected to the vacuum manifold, and evacuated while at −196 °C.

The hydrogen iodide was then brought to −20 °C, and vinylidene fluoride (previously condensed and measured in the gas tube described) was admitted to 150 psi. The reaction was very sluggish at first, but as product formed, it became faster and more exothermic. After about one-third of the vinylidene fluoride had been added, an ice bath was required to maintain the temperature at 40–45 °C. Cooling water was also fed through the coil, and the automatic feed valve was set for 150 psi. After 1 mol of vinylidene fluoride had reacted, the reaction stopped abruptly. The mixture was held for 0.5 h at 40–45 °C, 150 psi, to ensure complete consumption of the hydrogen iodide. The mixture was then cooled to 0 °C and vented through −80 °C traps to remove the excess vinylidene fluoride.

The trap contents and the main product were combined and washed at −10 °C with cold brine containing sodium bisulfite to reduce the iodine. It was then washed with ice water and dried with calcium chloride before distillation. It boiled very constantly at 45 °C. The yield in several experiments was 95% when stringent precautions were taken to prevent evaporative losses. The still residue, about 0.3% of the product, showed a GC trace suggestive of telomers of vinylidene fluoride with **2**, probably $CH_3CF_2(CH_2CF_2)_xI$, and 1,1-difluoro-1,2-diiodoethane from addition of iodine to vinylidene fluoride.

A large run[14] was made in the 2-gal autoclave, to which had been added 10 g of iodine. It was cooled to −40 °C and evacuated, and 5067 g of hydrogen iodide was added liquid phase from chilled cylinders. The vent from the autoclave was connected to two −80 °C traps in series, the contents of which were added to the autoclave at the end of the addition. The weight was determined from the loss in weight of the cylinders. Vinylidene fluoride was then added vapor phase from a tared cylinder to a pressure of about 150 psi, and the mixture was then warmed to 30 °C. When the reaction became exothermic, it was controlled by circulating chilled acetone from an external −80 °C bath through the internal cooling coils. When 2740 g had been added, the reaction stopped; about 2.5 h was required. The mixture was held for 0.5 h longer, then chilled to −40 °C. The autoclave was vented through a −80 °C condenser delivering into a chilled 12-L flask, and the product was poured into that flask and allowed to warm to room temperature under the −80 °C condenser. The product was then fractionated. The yield of constant-boiling **2** was 96%.

Telomerization of 2 with Tetrafluoroethylene. All of the exploratory work was done in the glass pressure bottles. The catalyst to be tested and the telogen were added to the reaction bottle, which was then attached to the vacuum manifold, chilled first to −80 °C, then to −196 °C, and evacuated. (Although we occasionally cooled directly from room temperature to −196 °C, or warmed from −196 °C to room temperature with a methanol bath, and never had a tube crack, safe practice dictates performing the heating or cooling in two steps.) The contents were then brought to the desired reaction temperature. Meanwhile, TFE was condensed in an evacuated tube and measured at −80 °C. It was then warmed to the desired pressure with an appropriate bath and fed to the reaction mixture as described above. Further details are given below. When the reaction was judged complete, the mixture was cooled to −20 °C, and the unreacted TFE was stripped out by vacuum transfer into a calibrated tube for measurement.[15] It was then discarded. Usually 0.5–0.7 mol of TFE was fed per mol of telogen.

The product was then transferred to distillation equipment and the unreacted telogen was removed at atmospheric pressure through a fractionating column packed with $\frac{3}{16}$ in. protruded stainless steel packing. The residue was then fractionated in vacuo.

No more will be said about the unsuccessful experiments mentioned in the Discussion section. Telomerization with benzoyl peroxide required at least 1 mol % of this initiator to achieve conversion of 0.5 mol of TFE per mol of **2** at 80 °C, 200 psi, ending at 90–95 °C, 275 psi. Smooth reaction occurred when the stirring was efficient. Several good

Table I. Properties of Telomers $CH_3(CF_2)_nI$, 3[a]

n	Bp, °C (Torr)	Mp, °C	Formula
1[b]	45.6 (760)		
3	95.0 (760)		$C_4H_3F_6I$
5	93 (172)		$C_6H_3F_{10}I$
7	94 (53)		$C_8H_3F_{14}I$
9	118 (38)	50	$C_{10}H_3F_{18}I$
11	125 (17)	79–80	$C_{12}H_3F_{22}I$
13[c]	155 (21)	113–114	$C_{14}H_3F_{26}I$
15	166 (15)[d]		

[a] Satisfactory values for microanalysis for C and H, and in most cases F and I, were obtained for these compounds. NMR spectra in CCl_3F and mass spectra were consistent with the structures. In addition, the homologues n = 2, 4, 6, and 8 were identified by GC/MS. [b] Known compound, ref 1. [c] The compounds n = 13 and 15 could not be separated completely by distillation or crystallization. [d] Not obtained pure.

Table II. Properties of Telomers $CH_3(CF_2)_nCH_2CH_2I$, 4[a]

n[b]	Bp, °C (Torr)	Mp, °C	Formula
3	101.3 (96)[c]		$C_6H_7F_6I$
5	114 (50)		$C_8H_7F_{10}I$
7	109 (10)	40.0–40.5	$C_{10}H_7F_{14}I$
9	131 (10)	70.0–70.5	$C_{12}H_7F_{18}I$
11	155 (12)	94–95	$C_{14}H_7F_{22}I$
13		122.0–122.5[d]	$C_{16}H_7F_{26}I$
15		133–134[e]	

[a] Satisfactory microanalyses for C, H, and I, and in some cases F, were obtained for these compounds. NMR spectra in CCl_3F and mass spectra were consistent with the structures assigned. [b] Some of the compounds n = 1, 2, 4, 6, and 8 were identified by GC/MS. [c] Also bp 164 °C (760 Torr); at this temperature, the iodide attacks the stainless steel packing. [d] Recrystallized from acetone. [e] Since the starting iodide was not pure, this product was a mixture of roughly equal amounts of n = 13 and 15.

runs were combined for fractional distillation. The progress of the fractionation was followed by GC analysis (see below). Intermediate cuts were redistilled to concentrate the impurities. GC/MS permitted identification of the following impurities: C_6H_5I, an iodobenzoic acid, an isomer of $IC_6H_4CF_2CH_3$ (action of $CH_3CF_2\cdot$ on iodobenzene), $H(CF_2)_5F$, $H(CF_2)_6F$, $CF_3CF_2CHFCF_2I$, $ICH_2CF_2CF_2I$, $ICF_2CF_2CH_2(CF_2)_3I$, and the telomer series with an *even* number of CF_2 groups mentioned in the Discussion section. Formation of most of these compounds obviously requires hydrogen abstraction by a growing radical, in some cases followed by iodine transfer. Since these compounds (except for iodobenzene) are formed in only trace amounts, hydrogen abstraction is not an important side reaction in this telomerization.

Thermal telomerization (no catalyst) with 2 was conducted at 195 °C in a 400-mL shaker tube.[16] Since no compressor for TFE was available, and since the vapor pressure of 2 at the reaction temperature was almost equal to the cylinder pressure of TFE, it was difficult to achieve significant conversion. Although telomers were formed (GC), thermal telomerization was not pursued when a superior method was found.

Exploratory experiments with *tert*-butyl peroxypivalate (Lupersol 11, supplied by Lucidol Co. as a 75% solution in mineral spirits) were conducted in glass as described. But safety considerations prohibited use of a large autoclave with TFE. Accordingly, 31 telomerizations were conducted by the following general procedure. The 400-mL shaker tube was chilled to −80 °C, and 580 g (chilled) of 2 was poured in. The catalyst was then added. In early runs, 5 g was used. Later the amount was reduced until the last 12 runs were made with only 0.3 g of this material (corresponding to 0.04 mol %). The bomb was sealed, weighed, pressure tested, and evacuated at −80 °C. Then 15 g of uninhibited TFE was added from a tared small cylinder on a balance. It was then heated to 50 °C; the pressure was 120–180 psi. Too rapid feed of TFE will cause a sudden exothermic reaction, with destruction of the catalyst, or worse. Near the end, the pressure was raised to 300 psi, the temperature to 70 °C. The total TFE fed was 160 g. The bomb was then reweighed, cooled to −80 °C, vented, and discharged into a cold bottle for refrigerated storage.

Several runs were combined and warmed to room temperature under a −80 °C condenser to separate dissolved TFE. Unreacted telogen was distilled out through a 1-m fractionating column fitted with protruded packing; it was 99.9% pure (GC) and was suitable for recycle. The telomers were separated by fractional distillation at reduced pressure (Table I).

In one such group, the following results were obtained. From a total of 10.905 kg of 2, 57.0 mol, and 3.568 kg of TFE fed, 35.7 mol, 0.627 mol/mol (by weight gain), 5.638 kg of telomers 3, $n \geq 3$, was obtained. Its composition on a weight basis was 34.6, 22.4, 17.4, 12.6, 7.1, and 6.0%, on a mole basis 47.5, 23.0, 14.2, 8.6, 4.0, and 2.7% for the respective telomers n = 3, 5, 7, 9, 11, and ≥13. Thus 0.518 mol of TFE (average) per mol of telogen was actually incorporated into products.

All the telomers 3 up to n = 11 were obtained pure. The telomer n = 13 was obtained in only 95% purity (contaminated by n = 15). The higher telomers decomposed at pot temperatures above 170–180 °C, and the telomer n = 13 melted at 113 °C. A specially designed column and thermostated stillhead would have permitted separation of pure telomers n = 13 and 15.

Telomerization of the telomer 3, n = 3, with Lupersol 11 by the above procedure was facile, and the product distribution was somewhat "sharper", i.e., the amounts of higher telomers fell off more rapidly, than with the telogen 2. "Thermal" telomerizations were performed without catalyst at 200 °C; the vapor pressure of this telogen was low enough (120 psi) to permit easy TFE feed. From a total of 2012 g (6.88 mol) of telogen and 532 g of TFE (mole ratio 0.723), 2532 g of product was obtained. Fractionation yielded, in addition to recovered telogen, 640 g, 46%; 307 g, 22%; 454 g, 32%; of the respective telomers n = 5, 7, and ≥9.[17] The product distribution was again sharper than with 2 because CH_3CF_2I transfers iodine less readily than does $CH_3(CF_2)_3I$.[11]

Analysis. GC analysis of the mixtures encountered in this work was conducted on DC-200 silicone oil (20% on Chromosorb P, 45–60 mesh), with helium as carrier gas, TC detector. Solid products were dissolved in trichlorotrifluoroethane (Freon 113) before injection. Areas were determined by triangulation; calibration factors were applied to give weight percent. To identify trace components, the desired peaks were trapped, then injected into a mass spectrometer. Identification was made by comparison to our extensive library of mass spectra of fluorocarbons. In some cases, structures were inferred from the molecular ion peak and the cracking pattern. I am indebted to Mr. Fulton G. Kitson for the mass spectral identifications.

^{19}F NMR was performed on a Varian instrument by Mr. Thomas E. Beukelman. Interpretation was facilitated by our extensive reference library.

Ethylene Insertion. Pure 3 was heated at about 195 °C under 200–250 psi ethylene pressure for 8–12 h. For example, 535 g of $CH_3(CF_2)_5I$ was charged to the 400-mL shaker tube, which was then sealed, pressure tested, evacuated at −80 °C, and heated to 195 °C (vapor pressure 55 psi). Ethylene was admitted, and the pressure was maintained at 250 psi for 8.5 h. No further pressure drop occurred, showing that 4 was incapable of reacting with additional ethylene under these conditions. The bomb was cooled, vented, and discharged. Some material was lost in the feed lines, so the material balance was only 95%. Two such runs were combined and fractionated, yielding 37 g. (3.4%) of unreacted 3 and 995 g (84%) of product 4. The 47 g of still residue was mostly 4, but it also contained the telomers $CH_3(CF_2)_5(C_2H_4)_mI$, m = 2, 3, 4, identified by GC/MS.

With the other iodides 3, 1–2% of starting material escaped conversion, and less than 1% of higher telomers were formed. Intermediate distillation cuts contained fragmentation products with fewer CF_2 groups than in 3. Thus from 3, n = 3, containing no detectable impurities, the following compounds were detected by GC/MS:

3, n = 1, 2
$CH_3(CF_2)_n(CH_2CH_2)_mI$
n = 1; m = 1
n = 2; m = 1, 5
n = 3; m = 1, 2, 4, 5, 8
n = 5; m = 1, 2, 3
n = 7; m = 1

In addition, 15, $CH_3(CF_2)_3H$, $CH_2{=}CHCH_2CH_2CF_2CF_2CHFCH_2Cl$, 1,2,3,3-tetrafluorocyclobutene, and $C_{31}H_{63}I$ were detected. Total impurities were less than 2% of the product; such is the sensitivity of the GC/MS method.

Table III. Properties of $CH_3(CF_2)_nCH_2CH_2OH$, 6[a]

n	Bp, °C (Torr)	Mp, °C	Formula
5	87 (10)		$C_8H_8F_{10}O$
7	104 (10)		$C_{10}H_8F_{14}O$
9	130 (10)	53–54	$C_{12}H_8F_{18}O$
11	150 (10)	95–96	$C_{14}H_8F_{22}O$
13[b]		157–158	$C_{16}H_8F_{26}O$

[a] Satisfactory microanalyses for C and H, and in two cases F, were obtained for these compounds, except for $n = 13$. NMR spectra in CCl_3F were consistent with the structures. [b] The analysis agrees well with a dihydrate. Anal. Calcd: C, 25.7; H, 1.6. Found: C, 25.7; H, 1.5. The product also contains 0.5% I. This alcohol made satisfactory acrylate and methacrylate.

Table IV. Properties of $CH_3(CF_2)_nCH_2CH_2OCOC(R)=CH_2$, 7[a]

n	Method[b]	Bp, °C (Torr)	Formula
		A. Acrylates, R = H	
5	KS	109 (11)	$C_{11}H_{10}F_{10}O_2$
9	TE	90 (0.2)	$C_{15}H_{10}F_{18}O_2$
13	TE	128 (0.5)[c]	$C_{19}H_{10}F_{26}O_2$
		B. Methacrylates, R = CH_3	
3	KS	106 (21)	$C_{10}H_{12}F_6O_2$
5	KS	118 (10)	$C_{12}H_{12}F_{10}O_2$
7	KS	95 (0.8)	$C_{14}H_{12}F_{14}O_2$
9[d]	KS	105 (0.5)	
13[e]	TE	160 (1.0)[f]	$C_{20}H_{12}F_{26}O_2$

[a] Satisfactory NMR and IR spectra, and microanalyses for C and H (and in two cases F) were obtained, except as noted. [b] KS = potassium salt displacement; TE = transesterification. [c] Also mp 103–104 °C. [d] Not obtained pure. [e] The product is about 95% pure by GC. The principal impurities are $n = 11$, 15 methacrylates and $n = 11$, 13, and 15 iodides and alcohols. The carbon analysis is 1.3% low. [f] Also mp 103.0–103.5 °C.

Oleum Solvolysis of 4 to 6. Typically, the iodide **4**, $n = 7$ (100 g, 0.192 mol) was added dropwise to 300 g of 65% oleum maintained at 40–45 °C during 1.5 h. The mixture was maintained in that range for an additional 1.5 h. The viscous, deep bluish-green[18] mixture was transferred to an addition funnel with a 10-mm bore stopcock and added slowly to 700 mL of stirred water below 80 °C. Sodium bisulfite solution was added to the hydrolysis mixture to reduce the iodine. The mixture, now about 30% sulfuric acid, was refluxed (109 °C) for 2 h under a *wide-bore* condenser to prevent plugging by the solid alcohol hydrate which steam distills. A long glass rod was used for pushing that solid back into the flask. The lower layer was boiled briefly with fresh water. The crude alcohol, 64 g, was combined with 188 g of alcohol similarly obtained from 241 g of iodide, dried by refluxing with benzene under a water separator, and fractionated. The pure alcohol weighed 210 g, 78%. The forerun and tail cut, 40 g, were slightly less pure. The total yield was nearly quantitative.

With the iodide **4**, $n = 13$, the mixture became very viscous after about half the iodide had been added, but then it became gradually thinner. After the 3-h heating period, a little water was added *very cautiously* to thin the material so it could be poured. After the hydrolysis (as described), the alcohol was dried at 110 °C but not distilled. The yield was 99%.

(Meth)acrylates 7. A. By Transesterification. The alcohol **6**, $n = 9$ (44.1 g, 0.0866 mol), was mixed with 26.1 g (0.261 mol) of ethyl acrylate, 30.5 mL of benzene, a small drop of nitrobenzene, and 87 mg of 3,3′,5,5′-tetramethyldiphenoquinone, and refluxed under a fractionating column to remove water as its benzene azeotrope; 7.5 mL of benzene was removed. Then 0.2 mL of tetraisopropyl titanate was added with a syringe, and the mixture was slowly distilled to remove the benzene–ethanol azeotrope, bp 68 °C. When the head temperature could not be maintained below 75 °C, an additional 0.1 mL of titanate was added to ensure complete reaction. The benzene and excess ethyl acrylate were distilled out (24 mL), and the ester was distilled very rapidly under vacuum, yield 47.0 g (96.2%). It contained traces of benzene, ethyl acrylate, and unchanged alcohol which could be removed by topping through a short column.

Table V. Properties of $CH_3(CF_2)_nCH_2CH_2OSO_2Cl$, 8[a]

n	Bp, °C (0.5 Torr)	MS[b]	Formula
3[c]	72	Unusual	$C_6H_7F_6ClO_3S$
5	94	Unusual	$C_8H_7F_{10}ClO_3S$
7	110	Normal	$C_{10}H_7F_{14}ClO_3S$

[a] Satisfactory NMR spectra and microanalyses for C, H, and Cl were obtained for these compounds. [b] See Discussion section for comments on mass spectrometry. [c] Also sulfur. Anal. Calcd: 10.4. Found: 10.1.

The alcohol **6**, $n = 13$ (38.9 g, 0.05 mol), was dried azeotropically by refluxing with 25 g of methyl methacrylate, 35 mL of benzene, a small drop of nitrobenzene, and 100 mg of the quinone, treated with 0.2 mL of tetraisopropyl titanate, and the mixture was fractionated to remove methanol–benzene below 60 °C. Then 0.2 mL of water was added to destroy the titanate, and the product was stripped and distilled. The solid was redistilled through a short Vigreux column and the center cut was analyzed. The yield was about 50% because of thermal polymerization during the second distillation.

B. Displacement with Potassium Methacrylate. A mixture of iodide **4** with 2–3 mol of dry potassium (meth)acrylate in *dry* (molecular sieves) *tert*-butyl alcohol was refluxed for 14 h in the presence of a trace of tetramethyldiphenoquinone inhibitor. Some iodide escaped reaction. The mixture was drowned in water, and the aqueous layer was extracted with Freon 113. The combined organic layers were washed with water, dried, and distilled. Separation of unchanged iodide and by-product alcohol from the ester was difficult with $n = 3, 5, 7$, but impossible with $n = 9$. Therefore, transesterification procedure A is preferred.

Chlorosulfates 8. Chlorosulfonic acid (2.2 mol) was added dropwise to 1.0 mol of iodide at 40–45 °C during 1 h. The mixture was then maintained at 45–50 °C for 1 h. The escaping sulfur dioxide and hydrogen chloride were removed in a flowing water scrubber, and subliming iodine was retained by a wide-bore air condenser. The crude chlorosulfate was separated from suspended iodine by filtration on a dry, tared, sintered-glass funnel. The glassware was rinsed with Freon 113, which was then chilled to −30 °C and used to wash the iodine filter cake. Iodine is almost insoluble in this solvent at −30 °C. Iodine was recovered almost quantitatively. The solvent was evaporated and the chlorosulfate was distilled at reduced pressure; a small amount of the more volatile $CH_3(CF_2)_nCH_2CH_2Cl$ was collected separately. The high-boiling residue was mostly the alkylsulfuric acid **5**, as shown by infrared and by titration.

The chlorosulfates were identified by elemental analysis and NMR. The high-resolution mass spectra described in the text were obtained by Mr. R. D. Brown.

Olefins. The olefins **9**, $n = 5, 7$, were isolated from the methacrylate preparations with potassium methacrylate, simply by fractional distillation of the forerun. The olefin, $n = 11$, was prepared by refluxing a mixture of 216 g (0.3 mol) of iodide **4**, $n = 11$, with 22 g (0.37 mol) of 85% KOH in 150 mL of 95% ethanol for 19 h. The mixture was drowned in water, and the olefin was washed twice with hot water. The distilled product weighed 170 g (98.6%).

This olefin was oxidized to **10**, $n = 11$, by adding a solution of 105 g (0.67 mol) of potassium permanganate in 600 mL of water (90 °C) dropwise to 108.4 g (0.20 mol) of olefin at 70 °C during 1.5 h; the mixture was held at 70 °C for another 1 h. Slow addition of 70 g (0.67 mol) of solid sodium bisulfite was begun. When about half had been added, the temperature rose suddenly to 90 °C and the mixture sprayed out of the flask. Most of it was recovered and returned to the flask for completion of the bisulfite addition. Then 325 mL of concentrated hydrochloric acid was added cautiously, followed by enough additional bisulfite to destroy the remaining manganese dioxide. The mixture was then heated to 90 °C and cooled; the solid acid was collected and washed with 6 N hydrochloric acid. The solid was distilled rapidly at 30 mm to remove inorganic salts. When the solid distillate was remelted, an upper aqueous layer formed. Careful cooling froze the organic layer, and the water was decanted. The solid was then redistilled. The forerun was discarded, and the acid **10**, $n = 11$, was collected at 172 °C (28 mm), mp 92–93 °C, yield 53.5 g. At least some of the yield loss is attributable to the eruption.

Anal. Calcd for $C_{13}H_4F_{22}O_2$: C, 25.6; H, 0.7. Found: C, 25.9, H, 1.0.

Table VI. Properties of $CH_3(CF_2)_nCH{=}CH_2$, 9[a]

n	Bp, °C (Torr)	Mp, °C
3[b]		
5	130 (760)	
7	110 (147)[c]	
11[d]	126 (27)	36–37
13	143 (20)	75–76
15[e]	142–157 (10)	91–92
17+[f]		

[a] The first compound was identified by GC/MS only; the second and third by NMR only. The fourth and fifth compounds gave satisfactory C and H microanalyses, as well as consistent NMR spectra. [b] Detected as a by-product from the reaction of **4**, $n = 3$, with potassium methacrylate. [c] Also bp 90 °C (51 mm). [d] Prolonged refluxing of **4**, $n = 11$, with excess pyridine caused only partial dehydroiodination. [e] The product was a mixture of roughly equal amounts of $n = 13$ and 15. [f] A mixture of olefins, $n = 11$–25, was prepared from the mixed **4** prepared with ethylene insertion into the still residues from **3**. The presence of these olefins was detected by the GC analysis, but they were not otherwise characterized.

Preparation of 1,1,2,2-Tetrafluoro-1,4-diiodobutane (12).[9] A 400-mL shaker tube (Hastelloy C) was charged with 509 g (2.0 mol) of iodine, evacuated, and mounted in its heater on the shaker. A little TFE was admitted, and the bomb was heated to 125 °C. Then TFE was fed as rapidly as possible consistent with maintaining the temperature below 160 °C. When the theoretical amount of TFE had been absorbed, the pressure rose rapidly to 150 psi. The bomb was cooled to 100 °C and held for 1 h under 150 psi TFE pressure. Then at −80 °C, 100 g (4 mol) of ethylene was condensed into it. It was reheated to 150 °C, pressure about 5000 psi, and held for 6–8 h at 150 °C and a further 6–8 h at 165 °C. The product, a mixture of solid and liquid, was cooled to 0 °C and filtered; the solid was washed with a little cold chloroform. The solids from four such runs melted variously at 112–115 °C. The combined chloroform washes were evaporated and chilled to remove more solid. The combined liquids (four runs) were distilled to remove 11 and the more volatile by-products, then pure **12**, and finally the 2:1 adduct. 1,1,2,2-Tetrafluorocyclobutane was a major by-product, and the following trace compounds were also identified by GC/MS: HCF_2CF_2I, $CH_2{=}CHI$, $CH_3CH_2CF_2CF_2CH{=}CH_2$, CH_3CH_2I, $HCF_2CF_2CH_2CH_2I$, $I(CF_2)_4I$, and ICH_2CH_2I. The yield of pure **12** was 1792 g (59%), bp 85 °C (23 mm), and 306 g (9%) of 2:1 adduct was formed. The yield might be improved by feeding ethylene gradually from a compressor at pressures lower than the 5000 psi used here; we had no compressor. The optimum temperature was not determined.

Borohydride Reduction of 12. A solution of 3.8 g (0.1 mol) of sodium borohydride in 100 mL of methanol containing 0.1 g of sodium hydroxide was added to a solution of 38.2 g (0.1 mol) of **12** in 100 mL of methanol at 0 °C during 1 h under nitrogen. The next day the mixture was drowned in water. The lower layer was washed with dilute sodium bisulfite solution and water, then dried ($CaCl_2$). The crude **13** contained about 20% of unchanged **12**, but otherwise only trace impurities. The yield was about 66%. The product was distilled, bp 78.5 °C (202 mm) or 56 °C (51 mm). The center cut was identified by NMR and mass spectrum as $ICH_2CH_2CF_2CF_2H$, **13**. The method is potentially valuable for reducing other fluoroalkyl iodides R_FI to R_FH.

Dehydroiodination. The diiodide **12** (76.4 g, 0.2 mol) was added during 12 min to a solution of 25 g (0.25 mol) of dry triethylamine in 50 mL of dry *tert*-butyl alcohol. The mixture was then heated slowly. Between 40 and 70 °C, it turned black. It was refluxed (82 °C) for 45 min, and a sample was drowned in dilute hydrochloric acid; half of the **12** had not reacted. An additional 25 g of triethylamine was added and the mixture was refluxed for 30 min. The mixture was drowned in dilute acid, and the lower layer was washed and dried (45 g), then distilled. The olefin cut weighed 23.4 g, accompanied by 11.5 g of starting **12** and 5.5 g of tarry residue. The olefin cut was fractionated to yield a host of volatile impurities in the forerun, and pure **14**, bp 90–91 °C (760 mm), yield 25%. It was identified by NMR and mass spectrum.

An attempt to eliminate hydrogen iodide from **12** with potassium hydroxide in isopropyl alcohol caused extensive destruction, with formation of $CH_2{=}CHCF_2CF_2H$, $CH_2{=}CHCF_2COOK$, and other products. The yield of olefin was miserable. Perhaps a strong base in an aprotic solvent (Me_2SO, dioxane) would effect a satisfactory elimination without attack on the other iodine atom.

Diimide reduction of **14** was accomplished by adding 0.2 mol of 95% hydrazine to a mixture of 20 g (0.079 mol) of **14**, 100 mL of methanol, and 0.2 g (2 mmol) of cuprous chloride. The temperature rose to 35 °C. The mixture was cooled strongly while 28.3 g (0.25 mol) of 30% hydrogen peroxide was added dropwise in 37 min at 30–40 °C. The yellow solution was stirred for 2 h at ambient temperature; a small lower layer was noted. The mixture was diluted with 500 mL of ice water containing 2 mL of concentrated hydrochloric acid, the mixture was extracted with three portions of o-dichlorobenzene, and the extract was stripped at 100 mm into a −80 °C trap until the solvent began to boil. The trap contents were then distilled. The center cut (2.1 g), bp 40–45 °C (150 Torr), was 81% $CH_3CH_2CF_2CF_2I$ (**15**), 8% **14**, and the balance other materials (NMR). The outer cuts totaled 1.9 g. The yield of **15** was 10% in this single attempt.

Acknowledgment. I am indebted to Mr. Walter G. Barber for skillful and imaginative technical assistance throughout this work. I am grateful to the individuals named for the specialized analytical services provided.

Registry No.—**2**, 420-47-3; **3** ($n = 3$), 61951-28-8; **3** ($n = 5$), 61915-74-0; **3** ($n = 7$), 61915-75-1; **3** ($n = 9$), 61915-76-2; **3** ($n = 11$), 61915-77-3; **3** ($n = 13$), 61915-78-4; **3** ($n = 15$), 61915-79-5; **4** ($n = 3$), 61915-80-8; **4** ($n = 5$), 61915-81-9; **4** ($n = 7$), 61915-82-0; **4** ($n = 9$), 61915-83-1; **4** ($n = 11$), 61915-84-2; **4** ($n = 13$), 61915-85-3; **4** ($n = 15$), 61915-86-4; **6** ($n = 5$), 61915-87-5; **6** ($n = 7$), 61915-88-6; **6** ($n = 9$), 61915-89-7; **6** ($n = 11$), 61915-90-0; **6** ($n = 13$), 61915-91-1; **7** (R = H; $n = 5$), 61915-92-2; **7** (R = H; $n = 9$), 57678-90-7; **7** (R = H; $n = 13$), 61915-93-3; **7** (R = Me; $n = 3$), 61915-94-4; **7** (R = Me; $n = 5$), 61915-95-5; **7** (R = Me; $n = 7$), 61915-60-4; **7** (R = Me; $n = 9$), 61915-61-5; **7** (R = Me; $n = 13$), 61915-62-6; **8** ($n = 3$), 61915-63-7; **8** ($n = 5$), 61915-64-8; **8** ($n = 7$), 61915-65-9; **9** ($n = 5$), 61915-66-0; **9** ($n = 7$), 61916-67-1; **9** ($n = 11$), 61915-68-2; **9** ($n = 13$), 61915-69-3; **9** ($n = 15$), 61915-70-6; **10** ($n = 11$), 61915-71-7; **12**, 755-95-3; **13**, 61915-72-8; **14**, 33831-83-3; **15**, 61915-73-9; vinylidene fluoride, 75-38-7; TFE, 116-14-3; ethylene, 74-85-1; ethyl acrylate, 140-88-5; methyl methacrylate, 80-62-6; potassium methacrylate, 6900-35-2.

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(11) R. D. Chambers, J.Hutchinson, R. H. Mobbs, and W. K. R. Musgrave, *Tetrahedron*, **20**, 497 (1964).
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(13) For references, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 257.
(14) I am indebted to Mr. J. L. Robinson for this experiment.
(15) The liquid in this tube is a mixture of TFE and telogen **2**. By holding it at −20 °C with the vent open, the TFE evaporated with little loss of **2**. The amount of unreacted TFE was determined by the difference in volume between the two liquid measurements.
(16) I am indebted to Mr. Samuel Hearn and his staff in our High Pressure Laboratory for performing the experiments in shaker tubes.
(17) The percentage figures are based on the total weight of telomers $n = 5$ and higher.
(18) The bluish color suggests the presence of I_2^+, discovered by R. J. Gillespie and J. B. Senior, *Inorg. Chem.*, **3**, 440 (1964), and E. E. Aynsley, N. N. Greenwood, and D. H. W. Wharmby, *J. Chem. Soc.*, 5369 (1963).

Stereochemistry of Dialkylcuprate Additions to Cyclopropylacrylic Esters. An Application to the Synthesis of (±)-Eremophilone

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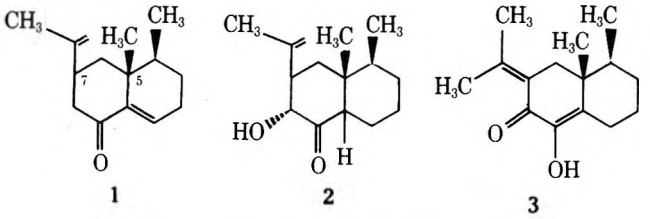
The details of the total synthesis of eremophilone (**1**) and its C-7 epimer **23** are discussed. The vicinal arrangement of cis dimethyl groups was achieved by the stereocontrolled addition of lithium divinylcuprate to 3,4-dimethylcyclohex-2-en-1-one. The C-7 center was created in a stereorandom fashion via a Claisen rearrangement one carbon removed from the nearest asymmetric site. This problem was solved in part by examining the stereochemistry of the addition of lithium diisopropenylcuprate to *syn*- and *anti*-cyclopropylacrylic esters **30b** and **36b**, respectively. The C-7 stereochemistry of the addition in the syn series was shown to favor the eremophilone stereochemistry (98/2), while the addition in the anti series was (85/15) in preference of the epieremophilone (**23**) stereochemistry. The stereochemical course of these reactions is discussed.

In 1932, Simonsen and co-workers[3a,4] reported the isolation of eremophilone (**1**), hydroxydihydroeremophilone (**2**), and hydroxyeremophilone (**3**) from the wood oil of *Eremophila mitchelli*, a tall shrub indigenous to the drier areas of New South Wales, Queensland, and South Australia. Adhering to the "inviolate" isoprene rule, Simonsen proposed the incorrect structure for eremophilone.[3a,b] Based upon a suggestion by Sir Robert Robinson that these substances might be nonisoprenoid compounds, Simonsen was able to propose and confirm the correct structure for eremophilone and its congeners.[3c-e] Some 15 years later Grant[5] confirmed the relative stereochemistry of hydroxydihydroeremophilone (**2**) by x-ray analysis. Shortly thereafter, Djerassi[6] provided the absolute stereochemistry of this trio by correlating hydroxyeremophilone (**3**) with material of known absolute stereochemistry. Since these three substances could be chemically interconverted, the absolute stereochemistry of the trio had been firmly established.



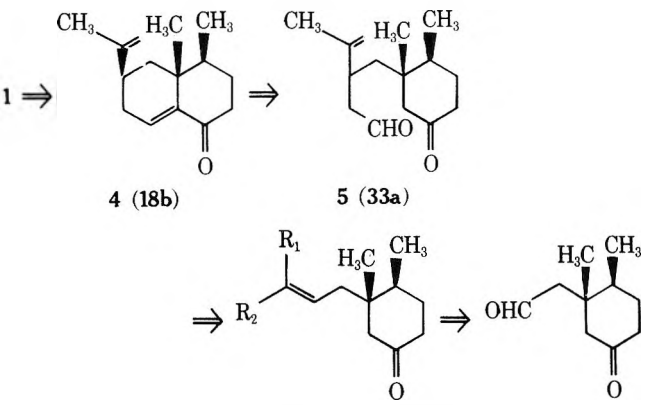
1 **2** **3**

During the 1960's and early 1970's substantial effort went into developing methods for constructing the eremophilane and valencane (7-*epi*-eremophilane) ring systems. Many of these investigations culminated in the synthesis of members of these classes.[7] In 1974, we reported[8] a synthesis which produced both eremophilone and 7-*epi*-eremophilone. The following year, McMurry published[9] a stereoselective synthesis of eremophilone from 7-epinootkatone. This paper details the results of our previous investigation and presents a method for controlling the stereochemistry at the C-7 site.[10]

Results and Discussion

Our antithetical analysis (Scheme I) considered enone **4** as a target molecule, since the Wharton reaction[11] formally allows for the transposition of enones. The keto aldehyde **5** necessary to prepare enone **4** is capable of synthesis by either a Claisen rearrangement employing the vinyl ether of alcohol **6a** or via conjugate addition of an isopropenyl moiety to unsaturated ester **6b**. Both of these compounds would ultimately be derived from a keto aldehyde of structure **7**. Two main problems presented themselves at the outset. First, it was necessary to find a method which would cleanly produce the cyclohexanone **7** bearing the cis arrangement of methyl groups

Scheme I



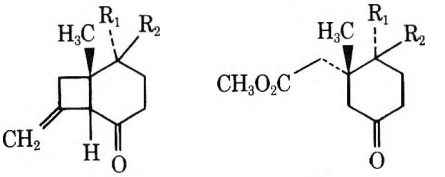
4 (18b) **5** (33a)

6a, $R_1 = CH_3$; $R_2 = CH_2OH$
b, $R_1 = H$; $R_2 = CO_2R$

7

and, secondly, whether or not it is possible for stereochemistry at the *pro*-C-7 center to be controlled by the *pro*-C-5 asymmetry.

The photoaddition of allene to cyclohex-2-en-1-ones has been applied successfully in polycyclic systems[12] with predictable stereochemistry as a means of formally adding acetaldehyde in a conjugate fashion. Corey has reported[13] the photoaddition of allene to cyclohexenone, providing the head-to-head adduct having an apparent cis-ring fusion, evidenced by the lack of epimerization upon prolonged exposure to pyridine. Irradiation of 3,4-dimethylcyclohexenone in the presence of allene at −78 °C provided a 4:1 mixture of photoadducts **8** (72% yield) displaying methyl singlets in their NMR spectrum at δ 1.23 and 1.12, respectively. The head-to-head regioselectivity was confirmed upon low-temperature ozonolysis in methanol, providing the methyl keto esters **9**, arising from Haller–Bauer cleavage of the intermediate cyclobutanone.[13] The high-field methyl singlets and doublets present in the NMR spectrum of keto esters **9** were in a ratio



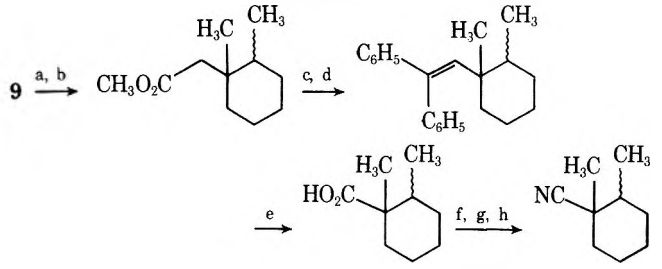
8 **9**

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

consistent with the photoadducts **8**, with the lower field signals predominating. The stereochemical assignments for these isomers were made by degradation of the keto esters to the

known isomeric *cis*- and *trans*-1,2-dimethylcyclohexylnitriles (Scheme II),[14] the cis isomer having been prepared from the

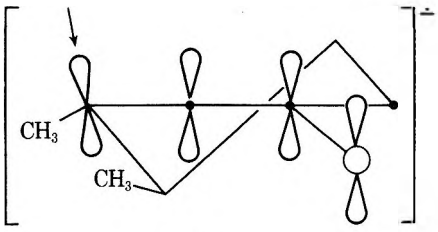
Scheme II



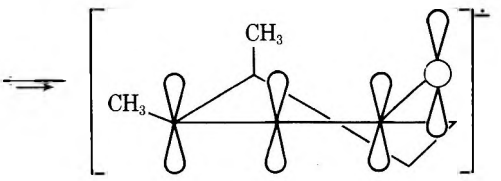
(a) KOH, NH_2NH_2, DEG; (b) CH_2N_2; (c) C_6H_5MgBr; (d) HOAc–H_2O, Δ (e) RuO_2, $NaIO_4$; (f) PCl_5; (g) NH_4OH; (h) $POCl_3$, Δ

Diels–Alder adduct of butadiene and tiglic acid.[15] NMR and VPC evidence indicated the same 4:1 ratio as in 8 and **9**, with the *trans*-1,2-dimethylcyclohexylnitrile being the major isomer.

Wiesner[16] has argued from evidence obtained from the photoaddition of allene and vinyl acetate to polycyclic cyclohexenones that the excited state of the enone has tetrahedral anionic character at the β position, being isoelectronic with the metal–ammonia reduction of similar species.[17] To our knowledge, no evidence has been brought to bare on this point concerning the stereochemistry in monocyclic systems.[18] It has been concluded[19] that the transition state radical anion from the metal–ammonia reduction of 3,4-dimethylcyclohexenone (84/16, trans/cis) is not completely sp^3 hybridized at the β position. The isomer ratios from the dissolving metal reduction (−33 °C) and the photoaddition (−78 °C) are similar, indicating a transition state with β-tetrahedral character (**10a**) lacking appreciable influence from $A^{1,2}$ interactions.[20]



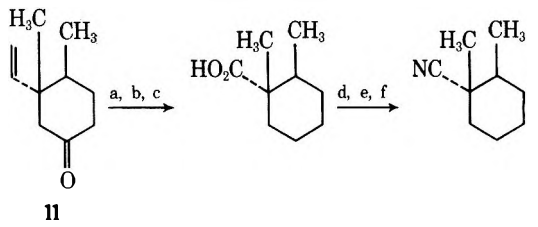
10a



10b

Since the photochemical route proved to be unsatisfactory for our needs, we sought another method which would solve this problem. The observation of Luong Thi and Riviere[21] that lithium diphenylcuprate adds to 4-methylcyclohexenone to provide a 97/3 mixture of *trans*- and *cis*-3-phenyl-4-methylcyclohexanone, respectively, taken in conjunction with evidence that cuprates add axially through a chair-like transition state[22] to cyclohexenones, argued that the 4-methyl group must be axially oriented in the transition state. Such an effect would lead to the conclusion that there would be appreciable $A^{1,2}$ interactions between the C(3)–H and C(4)–CH_3 if the latter were equatorial. Moreover, 3,4-dimethylcyclohexenone would be expected to provide a more selective reaction. This analysis proved to be correct, for when lithium divinylcuprate–tributyl phosphine complex[23] was reacted with 3,4-dimethylcyclohexenone a VPC homogeneous vinyl cyclohexanone **11** was obtained which had all the spectral attributes of a single diastereomer. In order to confirm the stereochemical integrity of this material, it was degraded as described in Scheme III, providing only *cis*-1,2-dimethylcyclohexylnitrile.

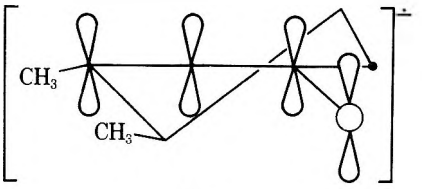
Scheme III



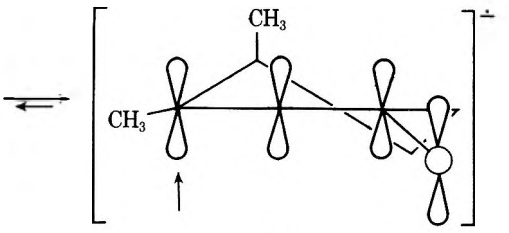
11

(a) KOH, NH_2NH_2, DEG; (b) O_3; (c) CrO_3; (d) PCl_5; (e) NH_4OH; (f) $POCl_3$, Δ

In striking contrast to the stereochemistry provided by the radical anion produced in the metal–ammonia reduction of 3,4-dimethylcyclohexenone, the cuprate addition, proceeding by an electron transfer process,[24] avoids $A^{1,2}$ interactions in a transition state **12b** with substantial sp^2 hybridization having the 4-methyl group axially oriented.



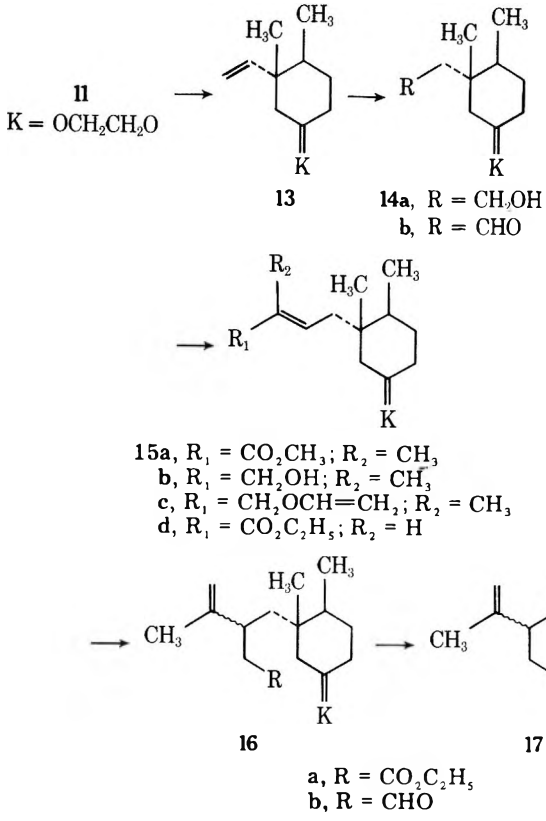
12a



12b

Having secured the methyl groups in the correct stereochemical arrangement, the elaboration of the vinyl group was accomplished by conventional ketalization of **11** followed by sequential hydroboration with disiamyl borane[25] and Collin's oxidation[26] to the desired ketal aldehyde[27] **14b**. Further confirmation for the diastereomeric purity of ketone **11** was obtained when alcohol **14a** was oxidized with Jones' reagent[28] followed by esterification with ethereal diazomethane to provide keto ester **9b**, whose NMR spectrum displayed a methyl singlet at δ 0.83 and a methyl doublet at δ 0.92, identical with the chemical shifts of the minor component in the diastereomeric keto esters **9** derived from the photochemical route.

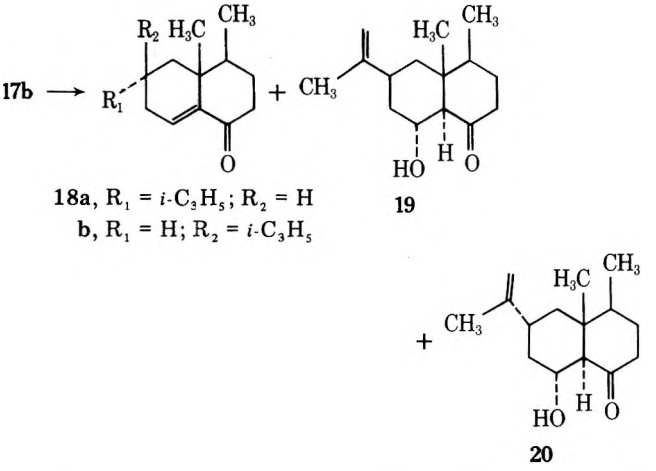
We were now in a position to answer the question concerning stereochemical control at the *pro*-C-7 center. To this end, ketal aldehyde **14b** was subjected to a Wittig reaction with α-carbomethoxyethylidenetriphenylphosphorane to provide the unsaturated ester **15a** consisting of a 15/1 (*E*/*Z*) mixture of isomers. The ester was reduced with lithium aluminum hydride by inverse addition to provide the ketal allylic alcohol **15b**, since the normal mode of addition gave appreciable amounts of conjugate reduction products. When the allylic alcohol was heated at 110 °C for 18 h in ethyl orthoacetate[29] in the presence of a catalytic amount of pivalic acid, the ketal ester **16a** was produced, displaying for the isopropenyl unit a three-proton singlet at δ 1.73 (vinylic methyl) and



a two-proton multiplet centered at δ 4.88 (vinyl) along with the expected ethyl resonances, confirming the introduction of the requisite functionality. Dilute acid hydrolysis of the rearrangement product liberated the ketone function providing keto ester **17a**. The NMR spectrum of this material revealed two quaternary methyl singlets in a ratio of approximately 60/40. It was apparent that stereochemical control in the rearrangement was virtually nonexistent. Moreover, when ketal aldehyde **14b** was converted to unsaturated ester **15d** followed by treatment with lithium diisopropenylcuprate and subsequent acid hydrolysis, the keto ester **17a** was produced. The NMR spectrum of this material was virtually identical with the product from the Claisen route.

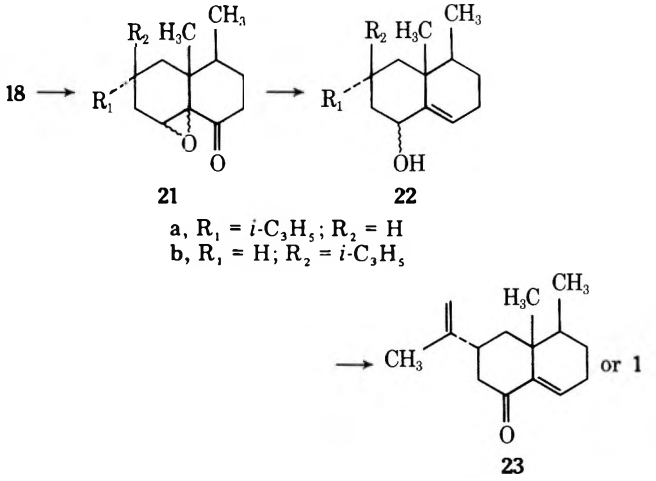
We chose at this juncture to examine the viability of the remaining stages of our synthetic plan (Scheme I) before reconsidering stereoselective development of the *pro*-C-7 center. To this end, mercuric acetate catalyzed exchange of allylic alcohol **15b** with *n*-butyl vinyl ether produced the vinyl ether **15c**, which upon heating at 175 °C for 12 min provided a diastereomeric mixture (~45/55) of ketal aldehyde **16b**. While this reaction was no more selective than the orthoacetate Claisen rearrangement, it conveniently provided the functionality necessary to accomplish the aldol condensation. Exposure of the ketals **16b** to aqueous acetic acid achieved deketalization without aldolization. Subsequent treatment of the keto aldehydes **17b** with sodium hydroxide in aqueous methanol provided a mixture of a single enone diastereomer **18** (1690 cm^{-1}, ~5%) and two hydroxy ketones (1710 cm^{-1}) **19** and **20** along with a variable minor amount of allylic alcohol **15b**, which was on occasion carried along when the crude Claisen product was utilized.

The aldol products proved to be resistant to or were destroyed by dehydration by traditional chemical means. However, when they were heated at 240–270 °C for 12 min a mixture of enones **18** was obtained with two distinct one-proton (enone vinyl) multiplets of nearly equal intensity in the NMR spectrum located at δ 6.40 and 6.18. The signal at δ 6.40 had the same chemical shift as the enone produced during the aldolization. Fractional crystallization of the



mixture of hydroxy ketones provided a single diastereomer, mp 94–95 °C, which displayed a doublet of triplets at δ 4.08 (J = 10 and 4 Hz) corresponding to the hydroxylmethine proton and consistent with an equatorial hydroxy group in either **19** or **20**. Upon thermolysis, this aldol provided the enone with the vinyl proton absorption at δ 6.18. Since no definitive information could be obtained at this point regarding the assignment of the stereochemistry of the isopropenyl group, it was necessary to explore the Wharton sequence to resolve this question by direct comparison with material from natural sources of known stereochemistry.

Reaction of the enone (δ 6.18) with alkaline hydrogen peroxide in aqueous methanol gave rise to an α,β-epoxy ketone **21** (1710 cm^{-1}), which upon exposure to hydrazine hydrate



in methanol–acetic acid gave a crude alcohol displaying a one-proton triplet at δ 5.56 (vinyl) in its NMR spectrum and the lack of carbonyl absorption in its infrared spectrum. Finally, oxidation under conditions which would not permit allylic isomerization, namely Collin's oxidation, provided eremophilone (**1**) (distinctly different from **18**) identical with a sample from natural sources[30] by thin layer chromatography, infrared, and NMR spectral comparison. The aldol product, mp 95–96 °C, could now be assigned structure **19** and its progeny **18b**, **21b**, and **22b**. Using the same synthetic sequence enone **18a** was transformed into 7-*epi*-eremophilone (**23**), different from eremophilone, but bearing gross spectroscopic similarities.

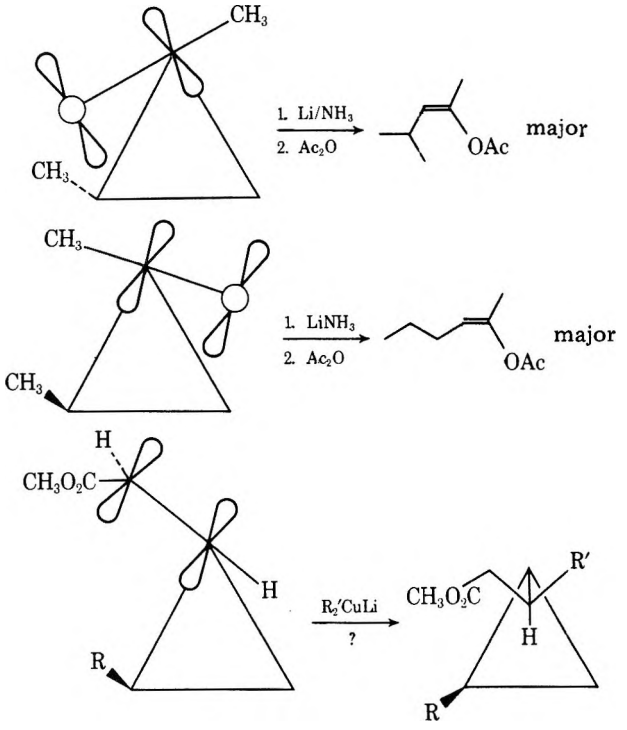
Although this approach allowed for eremophilone to be synthesized for the first time, a method was sought by which the stereochemistry at C-7 could be controlled employing the vinyl ketone **11**. It would not be necessary to convert synthetic material all the way to eremophilone (**1**) and 7-*epi*-eremophilone (**23**), since it was known that the enone **18b** had the vinyl hydrogen absorption at δ 6.18 and is converted to **1**, while

enone **18a** (δ 6.40) is transformed into **23**. These two intermediates could serve as relay compounds which would serve to define the stereochemical course of any new method.

The difficulty with the original synthesis was the failure of stereochemical control to be achieved at the *pro*-C-7 center. This was obviously due to the intercedence of the nonasymmetric center at *pro*-C-6. However, if the asymmetry at the *pro*-C-5 center could be used to generate the *pro*-C-6 center (i.e., a single diastereomer C-5, C-6), which could in turn be used to control the *pro*-C-7 center, a single diastereomer (C-5, C-7) would be achieved after the asymmetry has been removed at *pro*-C-6.

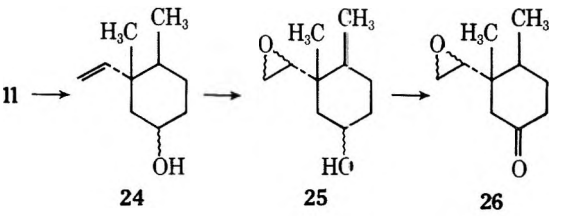
Dauben and Wolf[31] have shown that, when reduced with lithium–ammonia, methyl cyclopropyl ketones prefer a cisoid conformation in the transition state. Moreover, a cis alkyl group on the vicinal cyclopropane carbon alters the course of the bond cleavage (Scheme IV). Spectroscopic data indicates

Scheme IV

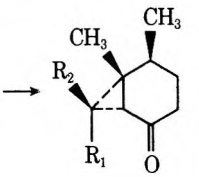


that the cisoid conformation of methyl cyclopropyl ketones is also preferred in the ground state,[32] while vinylcyclopropanes[33] and cyclopropylacrylic esters[34] prefer the transoid conformation. While the products from the methyl cyclopropyl ketone reductions are a reflection of the transition state geometry and not the ground state, it is imprudent to predict the course of kinetically controlled reactions from ground state geometries (Curtin–Hammett principle).[35] Given the generally high specificity in cuprate additions, the electron transfer process in both metal–ammonia reductions and cuprate additions,[24] and the similarity of ground and transition state geometries in the methyl cyclopropyl ketone reductions, it did not seem unreasonable that the mode of addition to a substituted cyclopropylacrylic ester would be as shown in Scheme IV. To test this possibility, a synthesis of the appropriate cyclopropylacrylic ester was undertaken.

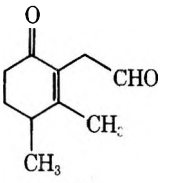
Reduction of vinyl ketone **11** with ethereal lithium aluminum hydride gave the alcohols **24**, which were successively oxidized with *m*-chloroperbenzoic acid to epoxy alcohols **25** and with chromium trioxide–dimethyl pyrazole complex[36] to a mixture of keto epoxides **26**. This sequence was necessitated by the fact that direct epoxidation of **11** gave preferential Baeyer–Villiger products, while buffered epoxidations[37] were slow and erratic. The epoxidation of vinyl ketal **13** was uncomplicated, but removal of the ketal group resulted in a complex mixture of reaction products. The cyclopropanation[38] proceeded smoothly by the dropwise addition of the epoxy ketones to KO-*t*-Bu/HO-*t*-Bu at room temperature, providing the syn and anti alcohols **27a,b** in a ratio of ~2.5/1, respec-



24 **25** **26**



27a, R_1 = CH_2OH; R_2 = H
b, R_1 = H; R_2 = CH_2OH
c, R_1 = CHO; R_2 = H
d, R_1 = H; R_2 = CHO
e, R_1 = E–CH=$CHCO_2CH_3$; R_2 = H
f, R_1 = H; R_2 = E–CH=$CHCO_2CH_3$



28

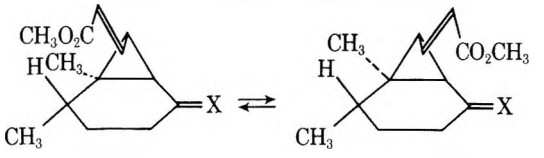
tively. The presence of the cyclopropane ring was confirmed by the appearance of a carbonyl frequency at ~1680–1675 cm^{-1} in both isomers. The syn–anti relationship was not able to be determined at this point with certainty, although the chromatographic polarity of the two alcohols was markedly different, the syn isomer presumably the less polar of the two compounds. On the assumption that the epoxide opening is S_N2-like, the isomer ratio would have been established at the epoxidation stage.

The stereochemistry of these isomers was placed on a firm foundation when the alcohols were oxidized to the cyclopropyl aldehydes with manganese dioxide.[39] The less polar alcohol provided an aldehyde which displayed an aldehyde proton (δ 9.70, d, J = 3 Hz), a three-proton doublet (δ 1.15, J = 6 Hz), a three-proton singlet (δ 1.20), and the remaining seven protons lying in the range δ 1.40–2.60. The more polar alcohol gave an aldehyde with an aldehyde proton doublet (δ 9.46, d, J = 4.5 Hz), the methyl singlet and doublet, and a five-proton array in the region δ 1.40–2.39. Shifted downfield from this area, in contrast with the other isomer, was a one-proton doublet (δ 2.47, J = 4.5 Hz) and a one-proton triplet (δ 2.84, J = 4.5 Hz). These latter resonances were assignable to the cyclopropane proton α to the ketone and aldehyde, respectively, in the anti isomer, each being deshielded by the other carbonyl. Irradiation of the aldehyde proton caused collapse of the triplet to a doublet, the doublet (δ 2.47) remaining unchanged. Alternatively, irradiation of the triplet caused the methine doublets to collapse to singlets. Attempts to interconvert the aldehyde isomers by epimerization resulted in decomposition of the substrates.

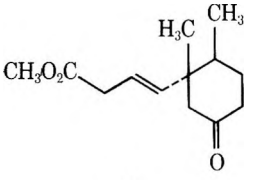
It is of interest that syn aldehyde **27c**[39] underwent partial thermal rearrangement upon VPC analysis (injection port 250 °C). Thermolysis of **27c** for 5 min at 250 °C under nitrogen produced aldehyde **28**, whose structure was assigned by NMR and IR spectroscopy. The presence of a three-proton doublet (δ 1.22, J = 7 Hz), a three-proton singlet (δ 1.92, vinylic

methyl), an unresolved two-proton singlet (δ 3.38, allylic methylene), and a one-proton triplet (δ 9.45, J = 2 Hz) in addition to carbonyl absorptions at 1770 (enone), 1725 (aldehyde), and 2720 cm^{-1} (aldehyde CH) was in full accord with the structural assignment. Such rearrangements are not without precedent,[40] although in this instance the initially formed tetrasubstituted double bond (C-3, C-4) migrates into conjugation with the ketone.

Since the syn alcohol **27a** was produced as the major and more readily available of the two isomers, the syn series was investigated first. Treatment of aldehyde **27c** with carbomethoxymethylenetriphenylphosphorane in methylene chloride at room temperature cleanly provided the unsaturated ester **27e** as a low-melting, crystalline solid. The α-olefinic proton (H_α) appeared in the NMR spectrum as a doublet (δ 5.89, J = 14.5 Hz), while the β-proton (H_β) appeared as a doublet of doublets (δ 6.76, $J_{\alpha,\beta}$ = 14.5 and $J_{\beta,\gamma}$ = 8 Hz) indicative of an E double bond and a transoid conformation of the side chain. Ethyl cyclopropylacrylate has been reported[34] to have a $J_{\beta,\gamma}$ = 9.4 Hz. While the coupling constant in this system arises from the weighted average[41] of $J_{trans} \cong 11$–12 Hz and $J_{gauche} \cong 4$ Hz,[42] the gauche conformations ($\theta_{\beta,\gamma} = 60°$) and s-cis ($\theta = 0°$) would all but be precluded from the syn ester conformations by interaction of the cyclohexane ring with the acrylic ester chain. Both half-chair conformations of the cyclohexane ring present transannular steric interactions between axial methylene hydrogens and H_β when the chain is maintained in the s-trans conformation ($\theta_{\beta,\gamma} = 180°$). The major conformers which would account for the observed coupling constant of J_{obsd} = 8 Hz would have to have $J(\theta_{\beta,\gamma})$ equal to or just less than 8 Hz. These conformers **29a** and **30a** need not have the same angle θ or be equally populated.



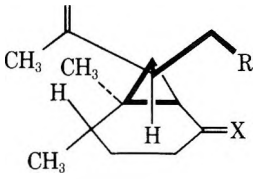
29a, X = O (**27e**) **30a**, X = O (**27e**)
b, X = OCH_2CH_2O– **b**, X = OCH_2CH_2O–



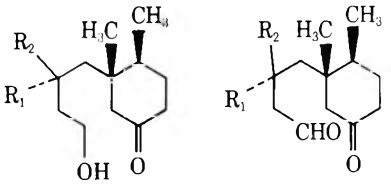
31

When the syn keto ester was reacted with lithium diisopropenylcuprate, a compound assigned structure **31** was obtained, displaying a ketone (1720 cm^{-1}) and a nonconjugated ester (1745 cm^{-1}) in its infrared spectrum. The NMR spectrum revealed the requisite methyl signals in addition to a broad two-proton singlet at δ 5.36 (vinyl H)[43] and 2.93 (allylic methylene). This type of reductive cleavage[44] is not unexpected in view of the electron transfer mechanism and is reminiscent of the course of the metal–ammonia reductions of methyl cyclopropyl ketones. In such a reaction, the conformation of the radical anion which effects cleavage would be related to ground state conformation **30a**, having the appropriate orbital overlap for reduction. In order to prevent reduction, it was considered necessary to mask the ketone as its ethylene glycol ketal[45] and, in addition, the ketal would be expected to favor conformer **30b**. The ketal, produced under carefully regulated conditions,[46] revealed a coupling constant of $J_{\beta,\gamma}$ = 10 Hz. This increase ($\Delta J_{\beta,\gamma}$ = 2 Hz) of the coupling constant is reasonable, since the ketal forbids conformations with small J values by restricting rotation about the C_β–C_γ bond and favors **30b** over **29b** (H_β/ketal interaction).

If the ketal function in **30b** were capable of accepting the role of the R group of the cyclopropylacrylic ester in our original proposal (Scheme IV), then the addition of the isopropenyl moiety to ketal **30b** should occur to provide adduct **32b**. When the cuprate addition was conducted followed by mild hydrolysis, a cyclopropyl keto ester (1686 and 1740 cm^{-1}), **32a** was obtained whose NMR spectrum displayed a



32a, R = CO_2CH_3; X = O
b, R = CO_2CH_3; X = OCH_2CH_2O
c, R = CH_2OH; X = O



33 **34**

a, R_1 = H; R_2 = i-C_3H_5
b, R_1 = i-C_3H_5; R_2 = H

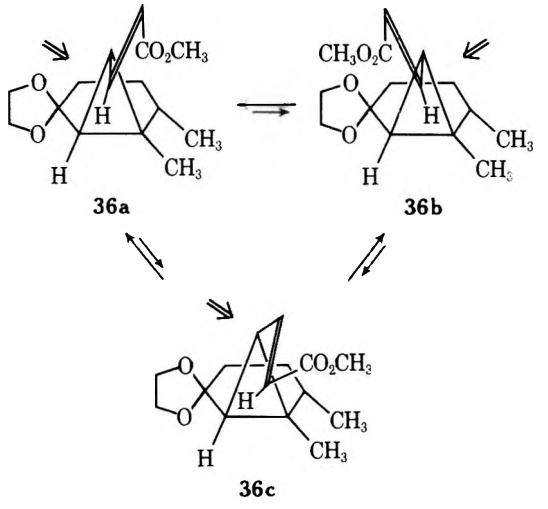
broadened two-proton singlet at δ 4.80 (H_2C=), three-proton singlets at δ 3.57 (CO_2CH_3) and 1.74 (vinylic CH_3), and a three-proton singlet and doublet (J = 7 Hz) both at δ 1.09. Although the chromatographic and spectroscopic evidence did not indicate diastereomers, it was necessary to convert this substance to either **18a** or **b** to confirm its purity.

Reduction of the crude ketal **32b** with lithium aluminum hydride followed by hydrolysis produced the cyclopropyl keto alcohol (3650–3390 and 1678 cm^{-1}) **32c**, which displayed the required methyl signals in its NMR spectrum. Reduction of the cyclopropyl ketone **32c** with lithium in liquid ammonia yielded a keto alcohol (3650–3200 and 1709 cm^{-1}) of gross structure **33** by the cleavage of the cyclopropyl bond overlapping with the ketone. Unraveling of the carbon framework as illustrated in **32** (bold lines) would give rise to the eremophilone stereochemistry. Collin's oxidation of **33a** provided the keto aldehyde **34a** [1725 cm^{-1} (br)], displaying a one-proton triplet (J = 3 Hz) at δ 9.22 in its NMR spectrum. Aldolization of the keto aldehyde followed by thermolysis gave enone **18b** in >98% isomeric purity by both NMR and VPC integration. Thus, as anticipated, the steric hindrance of the ketal allows for high selectivity in the cuprate addition step ($\Delta\Delta G^{\ddagger}_{273} > 2.1$ kcal).

The crystalline *anti*-cyclopropylacrylic ester **27f**, mp 93–94.5 °C, was prepared from the anti aldehyde by the method employed in the syn series. The NMR spectrum indicated a one-proton doublet of doublets at δ 6.59 (H_β, $J_{\alpha,\beta}$ = 15 Hz, $J_{\beta,\gamma}$ = 9 Hz), a one-proton doublet at δ 5.90 (H_α, $J_{\alpha,\beta}$ = 15 Hz), and a one-proton doublet of doublets at δ 2.60 (H_γ, $J_{\beta,\gamma}$ = 9 Hz, $J_{\gamma,\epsilon}$ = 4 Hz). The high-field signal for the cyclopropyl hydrogen was shifted downfield relative to the syn isomer, as was the case with the corresponding aldehydes. The β-proton experienced a slight ($\Delta\delta$ = 0.2 ppm) upfield shift relative to the syn isomer, which would be in accord with the larger coupling constant ($\Delta J_{\beta,\gamma}$ = 1 Hz) in the anti isomer, since the β-proton in the anti series would be in the shielding cone of the cyclopropane ring.[32a] Ketalization[47] of **27f** did not effect the value of $J_{\beta,\gamma}$, since the ketal group was sufficiently removed from the acrylate chain. The ketal was sequentially reacted with lithium diisopropenylcuprate, reduced with lithium aluminum hydride, and hydrolyzed to provide a cy-

clopropyl keto alcohol **35**. This material was reduced to the keto alcohol **33** with lithium ammonia, oxidized with Collin's reagent (**34**), aldolized, and thermolyzed to yield a 15/85 mixture of enones **18b** and **18a**. Structures **33b** and **34b** represent the stereochemistry of the predominant isomer derived from the *anti*-cyclopropyl ester ketal **36**.

If the transition state were to resemble the ground state in the addition reaction, the major stereoisomer would have to arise from the transoid conformation **36b** (or s-trans, $\theta_{\beta,\gamma}$ = 180°) or the gauche conformation **36c**, both presumably minor contributors to the ground state population. Conformation **36b** suffers from a peri-(H_β–CH_3) interaction, while **36c** has an incipient 1,6-H_β-cyclopropyl hydrogen interaction. If either **36b** or **36c** were involved in the product developing step it would be necessary for the rate constants for the reaction of these conformers to be significantly greater than for conformer **36a** to account for the observed product ratio. Such a difference would invariably be related to steric hindrance in **36a**. The fact that the hydrogen atoms of the ketal extend to the plane of cyclopropane ring, taken in conjunction with the bulk of the cuprate reagent, represent the only steric factors associated with **36a**.



On the other hand, if the transition state has tetrahedral character at C_β, then a transoid conformation would favor approach as in **36b** (relief of H_β–CH_3 interaction), while **36a** would develop such an interaction. It must be borne in mind that the ratio 15/85 only represents an energy difference of $\Delta\Delta G^{\ddagger}_{273} \sim 0.9$ kcal for the transition states in the anti series. Quite clearly the anti series has options open to it which are virtually excluded in the syn series.

The cuprate addition to these cyclopropylacrylic ester ketals allows for a stereoselective synthesis of eremophilone, since the syn alcohol **27a** is formed as the major stereoisomer and the syn ketal ester **30b** undergoes a highly selective cuprate addition. More importantly, the technique involving the cyclopropylacrylic esters introduces a method for controlling stereochemistry at isolated sites (i.e., no vicinal asymmetry) in carbon chains. The testing of this method in a natural products synthesis has also permitted the establishment of the stereochemistry of the reaction, information which would have been difficult to determine with simpler models.

Experimental Section

Melting points (corrected) were determined on a Fisher–Johns apparatus. Elemental analyses were performed by Atlantic Microlabs (Atlanta) and are within 0.3% of the theoretical composition. NMR spectra were determined on a Varian A-60 (60 MHz) or EM-360A (60 MHz), Perkin-Elmer R-32 (90 MHz), Jeolco Minimar (100 MHz), or Bruker HX-270 spectrometer. Chemical shifts are reported in δ (ppm) downfield from $(CH_3)_4Si$. IR spectra were recorded on a Perkin-Elmer 337 or Beckmann 4250 infrared spectrometer. Mass spectra were recorded on a Hitachi RMU-6E or AEI-MS-9 spectrometer. Gas chromatography was performed on a Varian 90-P(TC) using a 6 ft × ¼ in. 20% SE-30 on Anakrom 60/70 SD column or a Perkin-Elmer 3920 (FID) using a 5 ft OV-1 on Chrom W-HP (80–100) or 5 ft OV-225 GC-Q (100–120) column. Anhydrous magnesium sulfate was used for drying organic solutions, unless specified otherwise. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were dried by distillation from either $LiAlH_4$ or sodium benzophenone ketyl. Thick-layer chromatography was performed on Analtech 200 × 200 × 2 mm silica gel plates with fluorescent indicator.

Photoadducts 8. To a standard photochemical immersion unit[48] (Hanovia medium pressure 450-W lamp) equipped with a dry ice condenser was added 6.2 g (50 mmol) of 3,4-dimethylcyclohexenone[49] in 750 mL of ether. The reaction vessel was cooled in a dry ice–acetone bath followed by purging with N_2. The vessel was charged with ~15 mL of allene and irradiated for 22 h. After 4, 8, and 11 h, 15-mL portions of allene were added. The resulting solution was carefully concentrated and distilled [bp 62–64 °C (0.5 mm)] to provide a 4:1 mixture of photoadducts **8**. A sample collected by VPC showed: NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6 Hz), 1.12 (0.6 H, s), 1.23 (2.4 H, s), 3.21–1.09 (8 H, m), and 4.79 (2 H, m); IR (CCl_4) 1725 cm^{-1}.

Anal. ($C_{11}H_{16}O$): C, H.

Keto Esters 9. A solution of 3.68 g (24.4 mmol) of photoadducts **8** in 30 mL of CH_3OH was ozonized at −78 °C until the blue ozone color persisted. The solution was purged with N_2 and then treated with 3 mL of dimethyl sulfide[50] followed by warming to 25 °C over 4 h. The solvent was carefully removed and the residue taken up in ether. The organic solution was washed twice with water, dried, concentrated, and distilled to provide 3.3 g (69%) of the keto esters **9**: bp 86–88 °C (0.06 mm); IR (CCl_4) 1735 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (0.6 H, s), 0.92 (0.6 H, d, J = 7 Hz), 1.00 (2.4 H, d, J = 7 Hz), 1.07 (2.4 H, s), 2.62–1.37 (9 H, m), and 3.46 (3 H, s).

Degradation of Keto Esters 9 (Scheme II). To a mixture of 830 mg of potassium hydroxide and 2.2 g of 85% hydrazine hydrate in 10 mL of diethylene glycol maintained under N_2 was added 990 mg (5.0 mmol) of keto esters **9**. The mixture was brought to 130 °C for 30 min, during which time 2 mL of low-boiling liquid was removed. The remaining solution was heated for 3 h at 195–200 °C. The reaction mixture was cooled to 25 °C, poured into 25 mL of water, acidified with 3 N HCl, and extracted thoroughly with ether. The combined ether extracts were dried and treated with an excess of ethereal diazomethane. The excess diazomethane was decomposed after 5 min with HOAc and the ether solution was washed with saturated $NaHCO_3$ solution. The organic solution was dried, filtered, and concentrated to provide 800 mg (87%) of crude esters which were homogeneous by VPC: IR (CCl_4) 1735 cm^{-1}.

Phenylmagnesium bromide was prepared in the usual way from 1.57 g (10 mmol) of bromobenzene and 240 mg (10 mmol) of magnesium metal in 30 mL of dry ether. The crude esters, 800 mg (4.3 mmol), were dissolved in 5 mL of ether and added dropwise to the Grignard reagent over a period of 30 min. The reaction mixture was cautiously decomposed with saturated NH_4Cl solution after having stirred for 7 h. The phases were separated and the aqueous solution was thoroughly extracted with ether. The combined ether extracts were dried, filtered, and concentrated, affording a crude alcohol (IR (CCl_4) 3650–3200 and 3125–3050 cm^{-1}). The alcohols were dissolved in 12 mL of HOAc and 1 mL of H_2O, and the solution was refluxed for 10 h. The mixture was cooled to room temperature, diluted with ether, and washed with saturated $NaHCO_3$ until the washings were alkaline. The ether solution was dried, filtered, and concentrated to provide a crude residue exhibiting no hydroxy absorption in its infrared spectrum.

To a mixture of 80 mg of ruthenium dioxide in 10 mL of water was added 2.1 g of sodium metaperiodate in three portions over 10 min. To the stirred, clear yellow solution was added the crude dehydration product in 5 mL of acetone, producing an immediate black precipitate. Excess periodate was added as needed to maintain the yellow solution over a period of 60–70 h. The reaction mixture was filtered, the residue was washed with water and ether, and the resulting filtrates extracted three times with ether and once with chloroform. The combined organic fractions were extracted with 4 N NaOH solution and the extracts acidified with 3 N HCl. The acidic solution was extracted thoroughly with ether, dried, filtered, and concentrated to give 126 mg (0.8 mmol) of crude acids, which exhibited infrared absorptions at 3500–2300 and 1700 cm^{-1}.

The crude acids were added to 1.2 g (6 mmol) of phosphorus pentachloride in 5 mL of CH_2Cl_2 and stirred for 30 min. The mixture was cautiously poured onto 3 N NH_4OH at 0 °C. After 10 min, the layers were separated and the aqueous solution was extracted thoroughly with CH_2Cl_2. The combined extracts were dried, filtered, and con-

centrated. The residue was dissolved in 10 mL of ethylene dichloride containing 0.5 mL of $POCl_3$ and a trace of NaCl and refluxed for 18 h. The reaction mixture was cooled to 25 °C, washed with water, dried, filtered, and concentrated to afford 96 mg (14% overall) of a 4:1 mixture of *trans*- and *cis*-1,2-dimethylcyclohexylnitrile (IR 2245 cm^{-1}) having identical retention times (VPC) with authentic samples.[14]

Vinyl Ketone 11. To a stirred suspension of 28.5 g (0.15 mol) of cuprous iodide in 100 mL of dry ether maintained under N_2 at 0 °C was added 31.9 g (0.16 mol) of tri-*n*-butylphosphine at a rate such that the temperature did not exceed 20 °C. After the addition had been completed, the reaction mixture was allowed to stir at 25 °C until the milky CuI suspension was converted into a slightly cloudy yellow solution. The solution was cooled to −60 °C, followed by the addition of 150 mL (0.3 mol) of 2 M vinyllithium in THF (Ventron) via syringe at such a rate that the temperature did not exceed −30 °C. The resulting deep red-brown solution was cooled to −78 °C, stirred an additional 30 min, and followed by the addition of 12.6 g (0.1 mol) of 3,4-dimethylcyclohexenone in 50 mL of dry ether over a period of 45 min. After stirring the solution for an additional 1 h at −78 °C, the reaction mixture was allowed to warm to 25 °C and was subsequently poured into 200 mL of saturated NH_4Cl solution. After stirring for 1 h, the solution was thoroughly extracted with ether, dried, filtered, concentrated, and distilled to afford 15.0 g (98%) of ketone **11**, 95% pure by VPC analysis: bp 51–54 °C (0.3 mm); IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) δ 0.88 (3 H, s), 0.91 (3 H, d, J = 6 Hz), 4.83 (1 H, d, J = 15 Hz), 4.89 (1 H, d, J = 10 Hz), and 5.62 (1 H, d, J = 10 and 15 Hz).

Anal. (VPC sample) $C_{10}H_{16}O$: C, H.

Degradation of Vinyl Ketone 11. Employing the conditions for the Wolff–Kishner reduction and ozonolysis of photoadduct **8**, 1.3 g (8.5 mmol) of vinyl ketone **11** was successively converted to the crude 1,2-dimethylcyclohexane carboxaldehydes (Scheme III): IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ 9.35 (1 H, s). The crude aldehyde was dissolved in 10 mL of acetone at 0 °C, followed by the addition of 8 N Jones reagent[28] to the stirred solution until the reaction mixture gave a positive test with starch–iodide paper. After 30 min, the solvent was removed in vacuo and the residue taken up in water and thoroughly extracted with ether. The ether solution was extracted twice with 3 N KOH solution, the aqueous solution acidified with 3 N HCl, and thoroughly extracted with ether, dried, filtered, and concentrated to provide a crude acid: IR (CCl_4) 3500–3200 and 1700 cm^{-1}. The acid was transformed into the nitrile [IR (CCl_4) 2245 cm^{-1}] (vide supra) providing only *cis*-1,2-dimethylcyclohexylnitrile[14] (VPC) in 25% overall yield.

Keto Ester 9b. To a stirred solution of disiamylborane,[25] prepared from 240 mL (240 mmol) of 1 M borane in THF and 51 mL (480 mmol) of 2-methyl-2-butene in 300 mL of dry dimethoxyethane (DME) maintained at 0 °C under a N_2 atmosphere, was rapidly added 12.2 g (0.08 mol) of vinyl ketone **11** in 10 mL of DME. The reaction mixture was allowed to warm to 25 °C over 4 h, followed by cooling to 0 °C, and cautious treatment with 200 mL of 3 N aqueous NaOH solution followed by 120 mL of 30% H_2O_2. The solution was stirred overnight at 25 °C, poured onto 300 mL of water, and extracted thoroughly with ether. The ether extracts were dried, filtered, and concentrated.

The crude residue in 100 mL of acetone was added dropwise to a solution of 110 mL of 8 N Jones reagent in 400 mL of acetone at 0 °C. After the addition had been completed, the reaction mixture was stirred for 30 min and then concentrated in vacuo. The residue was thoroughly triturated with ether followed by extraction of the ether solution with 3 N NaOH. The aqueous solution was acidified with 3 N HCl, extracted with ether, dried, filtered, and partially concentrated (~100 mL) in vacuo. The ether solution was treated with a slight excess of ethereal diazomethane followed by removal of the solvent and distillation of the residue to provide 9.03 g (57%) of keto ester **9b**: bp 87–89 °C (1 mm); NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.92 (3 H, d, J = 7 Hz), and 3.47 (3 H, s).

Anal. ($C_{11}H_{18}O_3$): C, H.

Vinyl Ketal 13. A mixture of 14.50 g (0.095 mol) of vinyl ketone **11**, 11.8 g (0.19 mol) of ethylene glycol, and 910 mg (4.8 mmol) of *p*-toluenesulfonic acid in 400 mL of benzene was refluxed under nitrogen using a Dean–Stark trap. After 3 h, the solution was cooled to 25 °C, washed twice with 3 N NaOH, and once with water. The aqueous phase was extracted once with ether and the combined organic phases were dried, filtered, concentrated, and distilled to afford 16.8 g (90%) of vinyl ketal **13**: bp 71–73 °C (0.3 mm); IR (CCl_4) no carbonyl; NMR (CCl_4) δ 0.74 (3 H, d, J = 7 Hz), 0.95 (3 H, s), and 3.77 (4 H, s).

Anal. ($C_{12}H_{20}O_2$): C, H.

Ketal Aldehyde 14b. A stirred solution of 0.13 mol of disiamylborane in dry THF was prepared at 0 °C (vide supra). After 1 h, a solution of 16.8 g (0.086 mol) of vinyl ketal **13** in 30 mL of dry THF was added over a period of 5 min, after which the solution was allowed to warm to 25 °C and stirred for an additional 4 h. The solution was cautiously treated at 0 °C with 129 mL of 3 N NaOH followed by 100 mL of 30% H_2O_2 and allowed to warm to 25 °C over 18 h. The organic solvent was removed in vacuo and the aqueous solution was thoroughly extracted with ether. The ether solution was washed twice with water, dried, filtered, concentrated, and azeotroped in vacuo with benzene. The crude ketal alcohol **14a** (18.3 g, ~100%) had an NMR spectrum virtually identical with a sample of alcohol prepared in another experiment which had the following physical properties: bp 98–102 °C (5 μm); IR (CCl_4) 3650–3100 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 6 Hz), 0.91 (3 H, s) 3.73 (2 H, t, J = 7 Hz), and 3.86 (4 H, m).

Anal. ($C_{12}H_{22}O_3$): C, H.

Using purified solvents,[26b] 109.0 g (1.38 mol) of pyridine was added dropwise over a period of 5 min to a suspension of 68.8 g (0.69 mol) of chromium trioxide in 2.5 L of CH_2Cl_2. After stirring the mixture for 2 h at 25 °C, 18.3 g (0.086 mol) of the crude ketal alcohol **14a** in 50 mL of methylene chloride was added over a period of 5 min, after which the reaction mixture was stirred for 18 h. The solvent was removed followed by trituration of the residue with ether and filtration over Celite in vacuo. The residue was washed several times with ether and the combined ether fractions were concentrated and distilling providing 12.8 g (70%) of ketal aldehyde **14b**: bp 83–85 °C (5 μm); IR (CCl_4) 2725 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.96 (4 H, s), 2.38 (2 H, d, J = 4 Hz), and 9.95 (1 H, t, J = 4 Hz).

Anal. ($C_{12}H_{20}O_3$): C, H.

Ketal Ester 15a. A mixture of 4.35 g (20.5 mmol) of ketal aldehyde **14b** and 7.83 g (22.5 mmol) of α-carbomethoxyethylidenetriphenylphosphorane[51] in 100 mL of benzene was refluxed for 24 h. The cooled reaction mixture was concentrated in vacuo to a viscous oil, which crystallized upon trituration with 25 mL of hexane. The mixture was filtered and the residue washed thoroughly with hot hexane. The combined hexane fractions were concentrated and distilled to afford 5.77 g (91%) of a 15/1 (*E*/*Z*) mixture of ketal esters **15a**: bp 115–122 °C (6 μm); IR (CCl_4) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.81 (3 H, br s), 2.11 (2 H, br d, J = 8 Hz), 5.89 (0.06 H, br t, J = 8 Hz), and 6.75 (0.94 H, dt, J = 1.5 and 8 Hz) (irradiation at δ 1.81 causes collapse to a broad singlet).

Anal. ($C_{16}H_{26}O_4$): C, H.

Ketal Ester 15d. To a stirred suspension of 50 mL of dry DME containing 1.0 g (20 mml) of sodium hydride (50% dispersion in mineral oil), which had been washed twice with 5-mL portions of DME, maintained at 25 °C under N_2 was added dropwise 4.5 g (20 mmol) of ethyl diethylphosphonoacetate[52] in 25 mL of DME. To the resultant clear yellow solution was added 3.8 g (18.0 mmol) of ketal aldehyde **14b** in 15 mL of DME over 15 min (exothermic). The reaction mixture was stirred for 18 h at 25 °C and then concentrated in vacuo. The residue was dissolved in ether, washed with 3 N NaOH, dried, concentrated, and distilled to afford 4.7 g (90%) of ketal ester **15d**: bp 110–115 °C (8 μm); IR (CCl_4) 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 2.11 (2 H, d, J = 8 Hz), 3.82 (4 H, m), 4.10 (2, H, q, J = 7 Hz), 5.69 (1 H, d, J = 16 Hz), and 6.82 (1 H, dt, J = 8 and 16 Hz).

Anal. ($C_{16}H_{26}O_4$): C, H.

Allylic Alcohol 15b. To a stirred solution of 5.1 g (18.0 mmol) of ketal ester **15a** in 100 mL of ether maintained under N_2 at 0 °C was added 800 mg (21 mmol) of lithium aluminum hydride in five portions over a period of 5 min. The reaction mixture was stirred at 25 °C for 22 h, followed by cooling to 0 °C and cautious decomposition with saturated Na_2SO_4 solution. The ether layer was separated and the aqueous layer extracted thoroughly with ether. The combined extracts were dried, concentrated, and distilled to afford 4.07 g (95%) of allylic alcohol **15b**: bp 115–120 °C (5 μm); IR (CCl_4) 3620–3100 cm^{-1}; NMR ($CDCl_3$) δ 1.64 (3 H, br s), 3.86 (4 H, m), 3.95 (2 H, br s), and 5.41 (1 H, br t, J = 8 Hz).

Anal. ($C_{15}H_{26}O_3$): C, H.

Keto Esters 17a (via orthoacetate Claisen rearrangement). A mixture of 2.1 g (8.3 mmol) of allylic alcohol **15b** and 40 mg (0.4 mmol) of pivalic acid was heated in 10 mL of ethyl orthoacetate at 110–120 °C for 18 h under an atmosphere of N_2 with the occasional removal of low-boiling solvent. The reaction mixture was cooled, diluted with ether, washed with saturated $NaHCO_3$ solution, dried, and concentrated in vacuo to afford 2.5 g (93%) of crude ketal ester **16a**: NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.73 (3 H, s), 3.96 (4 H, m), 4.17 (2 H, q, J = 7 Hz), and 4.88 (2 H, m).

A sample [1.1 g (3.4 mmol)] of the crude ketal was dissolved in 9 mL of ethanol and 3 mL of 0.3 N HCl and stirred for 24 h at 25 °C. The mixture was diluted with water, thoroughly extracted with ether, backwashed with saturated $NaHCO_3$ solution, dried, filtered, con-

centrated, and distilled affording 850 mg (86%) of keto esters **17a**: bp 110–115 °C (5 μm; Kugelrohr); IR (CCl_4) 1735 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (1.2 H, s), 0.73 (1.8 H, s), 0.78 (1.8 H, d, J = 6 Hz), 0.92 (1.8 H, d, J = 6 Hz), 1.20 (3 H, t, J = 7 Hz), 1.65 (3 H, s), 4.00 (2 H, q, J = 7 Hz), and 4.70 (2 H, m).

Anal. ($C_{17}H_{28}O_3$): C, H.

Keto Esters 17a (via cuprate). To a stirred suspension of 1.0 g (0.14 mol) of sliced lithium wire (1.1% Na) in 30 mL of dry ether maintained under an argon atmosphere at 25 °C was added, dropwise over a period of 1 h, 5.2 g (55.0 mmol) of 2-bromopropene.[53] After the addition had been completed, the mixture was stirred at RT for 18 h. The reaction mixture was transferred via syringe to a heavy-walled serum-capped centrifuge tube. The suspension was centrifuged and the supernatant solution was transferred to a second tube. The solution was standardized by NMR integration of the isopropenyl signals of a known volume aliquot against a weighted amount of benzene or biphenyl (1.1 M).

To a stirred suspension of 4.80 mg (2.5 mmol) of CuI in 25 mL of ether at 0 °C (under N_2) was added 4.5 mL (5.0 mmol) of 1.1 M isopropenyllithium. After 10 min, 282 mg (1.0 mmol) of ketal ester **15d** in 6 mL of ether was added dropwise over 5 min. After an additional 10 min, the solution was allowed to warm to 25 °C and poured onto an equal volume of saturated NH_4Cl solution. The mixture was stirred for 30 min and then thoroughly extracted with ether, dried, filtered, and concentrated. Deketalization (vide supra) provided a sample (VPC) of keto ester **17a** identical (NMR and VPC retention time) with the material prepared by the orthoacetate rearrangement.

Vinyl Ether 15c. A mixture of 1.5 g (5.9 mmol) of allylic alcohol **15b** and 30 mg of mercuric acetate were refluxed in 15 mL of butyl vinyl ether with occasional removal of the vapor head. Refluxing of the solution was continued for 18 h with the addition of 30-mg portions of mercuric acetate after 2 and 4 h. The reaction mixture was cooled, diluted with 30 mL of ether, and washed with 15 mL of cold saturated $NaHCO_3$ solution. The aqueous phase was backwashed with ether and the combined ether extracts were dried, filtered, concentrated, and distilled to provide 1.6 g (76%) of vinyl ether **15c**: bp 106–110 °C (5 μm); NMR ($CDCl_3$) δ 1.60 (3 H, br s), 1.96 (2 H, br d, J = 8 Hz), 3.80 (4 H, m), 4.27–3.85 (2 H, m), 5.42 (1 H, br t, J = 7 Hz), and 6.34 (1 H, dd, J = 7 and 14 Hz).

Anal. ($C_{17}H_{28}O_3$): C, H.

Enone 18a and Hydroxy Ketone 19. Vinyl ether **15c**, 5.0 g (17.8 mmol) (contaminated with 10–15% of **15b**), maintained under an atmosphere of N_2 was heated neat for 12 min at 175 °C. The crude product revealed the following spectroscopic data: IR (CCl_4) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (3 H, br s), 2.33 (1 H, m), 3.83 (4 H, m), 4.75 (2 H, m), and 9.50 (1 H, t, J = 3 Hz). The crude ketal aldehydes **16b** were stirred for 18 h in 72 mL of 80% aqueous HOAc. The solution was poured onto ice and carefully neutralized with 4 N NaOH while maintaining the temperature below 10 °C. The resulting solution was thoroughly extracted with ether, dried, filtered, and concentrated to give 3.1 g (74%) of crude keto aldehydes **17b**: IR (CCl_4) 1725 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 4.88–4.79 (2 H, m), 9.25 (0.5 H, t, J = 3 Hz), and 9.22 (0.5 H, t, J = 3 Hz).

The crude keto aldehydes **17b** were dissolved in 60 mL of methanol and 36 mL of 0.5 N aqueous NaOH at 0 °C under N_2. The initial yellow solution was allowed to warm to 25 °C over 18 h, by which time the solution had turned red. The solution was reduced to one-half its volume in vacuo and poured into an equal volume of water. The aqueous mixture was thoroughly extracted with ether, dried, filtered, and concentrated, providing 2.6 g of crude product. Chromatography of 1 g of this crude material on silica gel (35 g) using benzene as an eluent afforded three fractions.

The early eluents gave 50 mg (~5%) of enone **18a**: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.00 (3 H, d, J = 6 Hz), 1.75 (3 H, s), 4.73 (2 H, br s), and 6.40 (1 H, m).

The second material eluted was a mixture of hydroxy ketones **19** and **20** (600 mg): MS m/e 70 eV (rel intensity) 236 (32), 218 (40), 203 (22), 177 (42), 175 (32), 161 (32), 125 (100), 107 (38), 93 (34), 83 (54), 69 (60), and 55 (100). Trituration of this mixture with hexane afforded ketol **19**: mp 94–95 °C; IR (CCl_4) 3600–3200 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (3 H, s), 0.83 (3 H, d, J = 7 Hz), 1.68 (3 H, s), 4.08 (1 H, dt, J = 4 and 10 Hz), and 4.60 (2 H, br s).

Anal. ($C_{15}H_{24}O_2$): C, H.

The final eluent afforded 250 mg of allylic alcohol **15b**.

Enones 18. A 400-mg (1.7 mmol) sample of the ketol mixture **19** and **20** was heated under N_2 for 10 min at 250–270 °C (Wood's metal bath). The flask was cooled to 25 °C and the reaction mixture purified (TLC, double elution, C_6H_6) to afford 126 mg (34%) of enones **18a** and **18b** homogeneous on TLC and separable on VPC (OV-1): IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.06 (6 H, m), 1.73 (3 H, br s), 4.72 (2 H, br s), 6.18 (0.5 H, m), and 6.40 (0.5 H, m); MS m/e 70 eV (rel intensity), 218 (100), 203 (46), 177 (30), 176 (54), 164 (24), 163 (22), 162 (52), 148 (35), 136 (40), 134 (43), 119 (62), 107 (47), 105 (56), 93 (41), 91 (44), 79 (35), 77 (30), and 55 (36).

Anal. (evap dist/1μm) ($C_{15}H_{22}O$): C, H.

Epoxy Ketones 21. To a stirred solution of 126 mg (0.55 mmol) of enones **18** in 3 mL of CH_3OH maintained under N_2 at 15 °C was added 0.4 mL (3.3 mmol) of 30% H_2O_2. To this solution was added 0.05 mL (0.27 mmol) of 6 N aqueous NaOH in three portions over 30 min. The solution was stirred for 18 h at 25 °C and then poured into a solution of saturated Na_2SO_3 at 0 °C. The aqueous solution was extracted thoroughly with ether, dried, filtered, and concentrated to afford 123 mg (95%) of crystalline residue. The material was recrystallized to provide the epoxy ketones **21**: mp 56.5–58.5 °C (ether–hexane); IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.92–1.06 (6 H, m), 1.69 (3 H, s), 3.04 (0.5 H, d, J = 5 Hz), 3.24 (0.5 H, m), and 4.65 (2 H, br s).

Anal. ($C_{15}H_{22}O_2$): C, H.

Eremophilone (1) and 7-*epi*-Eremophilone (23). A stirred methanol solution of 127 mg (0.5 mmol) of epoxy ketones **21** maintained at 0 °C under N_2 was treated with 0.15 mL (4.0 mmol) of 85% hydrazine hydrate and 1 drop of acetic acid.[11] The solution was stirred for 8 h, during which time gas evolution was observed. The reaction mixture was diluted with ether, washed with water, dried, filtered, and concentrated to afford 115 mg of a yellow oil which was purified (TLC, C_6H_6) to provide 70 mg of allylic alcohols **22**: NMR ($CDCl_3$) δ 4.31 (1 H, m, >CHOH), 4.67 (2 H, br s), and 5.57 (1 H, m, =CHCH$_2$).

The crude alcohols in 1 mL of purified CH_2Cl_2[26b] were added to a stirred solution of 1.5 mmol of CrO_3·py complex in 6 mL of purified CH_2Cl_2 maintained under a N_2 atmosphere. After stirring for 1.5 h, the solvent was removed in vacuo and the residue was triturated with ether with subsequent filtration in vacuo through a Celite pad. The residue was thoroughly washed with ether, and the ether fractions combined and concentrated to afford 40 mg of an oil. The material was purified (TLC, C_6H_6), affording 15 mg of a mixture of enones **1** and **23**. Analytical thin layer chromatography [hexane (triple elution), 10% ethyl acetate–benzene, and benzene] showed the mixture to have the same R_f value as eremophilone obtained from natural sources:[30] IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.90–1.01 (6 H, m), 1.74 (3 H, m), 4.71 (2 H, m), 6.39 (0.5 H, t, J = 3 Hz), and 6.52 (0.5 H, t, J = 3 Hz);[54] MS m/e 70 eV ($C_{15}H_{22}O$), 218.16705 (calcd), 218.16643 (obsd).

The hydroxy ketone **19** was converted to eremophilone via the sequence **19** → **18b** → **21b** → **22b** → **1** in 15% overall yield.

Enone **18b**: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6 Hz), 0.91 (3 H, s), 1.75 (3 H, s), 1.10–2.62 (10 H, m), 4.73 (2 H, br s), and 6.18 (1 H, m).

Epoxide **21b**: IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.96 (1 H, d, J = 5 Hz) and 4.58 (2 H, br s).

Allylic alcohol **22b**: NMR ($CDCl_3$) δ 5.56 (1 H, t, J = 4 Hz).

Eremophilone (**1**): IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (6 H, m), 1.75 (3 H, s), 4.72 (2 H, m), and 6.56 (1 H, t, J = 3 Hz). The synthetic sample was identical with eremophilone (**1**) from natural sources by solution infrared and nuclear magnetic resonance spectroscopy.

Enone **18a** was converted to 7-*epi*-eremophilone **23** in 20% overall yield via the sequence **18a** → **21a** → **22a** → **23**.

Epoxy ketone **21a**: IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.03 (3 H, d, J = 6 Hz), 1.72 (3 H, s), 3.26 (1 H, d, J = 3 Hz), and 4.67 (2 H, m).

Allylic alcohol **22a**: NMR ($CDCl_3$) δ 4.30 (1 H, t, J = 2 Hz), 4.67 (2 H, br s), and 5.54 (1 H, t, J = 3 Hz).

7-*epi*-Eremophilone **23**: IR (CCl_4) 1690 cm^{-1}; NMR (CCl_4) δ 0.94 (6 H, m), 1.74 (3 H, s), 4.71 (2 H, br s), and 6.39 (1 H, t, J = 3 Hz).

Vinyl Alcohols 24. To a stirred suspension of 1.60 g (0.042 mol) of lithium aluminum hydride in 300 mL of dry ether was added dropwise 12.64 g (0.083 mol) of vinyl ketone **11** dissolved in 100 mL of dry ether over a period of 1 h. After the addition had been completed, the reaction mixture was stirred an additional 1 h, then cautiously decomposed with saturated aqueous Na_2SO_4, followed by the addition of anhydrous Na_2SO_4. The white granular suspension was filtered in vacuo through Celite, the filtrate concentrated and distilled to provide 11.08 g (86%) of vinyl alcohols **24**: bp 82–88 °C (1 mm); IR ($CHCl_3$) 3650–3100 cm^{-1}; NMR ($CDCl_3$) δ 0.68–1.00 (6 H, m), 2.74 (1 H, m), and 4.86–6.40 (3 H, m).

Anal. ($C_{10}H_{18}O$): C, H.

Epoxy Alcohols 25. To a stirred solution of 4.62 g (0.030 mol) of vinyl alcohols **24** in 200 mL of CH_2Cl_2 at 5 °C was added 7.24 g (0.032 mol) of 75% *m*-chloroperbenzoic acid. After the acid had dissolved, the solution was stirred at 25 °C for 21 h. The reaction mixture was

washed successively with 50 mL of 10% Na_2SO_3, 100 mL of 1% NaOH, and 100 mL of H_2O. The organic solution was dried, filtered, concentrated, and distilled (Kugelrohr) to provide 4.67 g (91%) of epoxy alcohols **25**: bp 90–100 °C (0.8 mm); IR ($CHCl_3$) 3700–3200 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (1 H, br s), and 2.46–2.83 (2 H, m, epoxide H).

Anal. ($C_{10}H_{18}O_2$): C, H.

Epoxy Ketones 26. To a stirred suspension of 9.30 g (0.093 mol) of CrO_3 in 310 mL of CH_2Cl_2 at 25 °C was added 8.90 g (0.093 mol) of 3,5-dimethylpyrazole.[36] After stirring the dark solution for 30 min, 6.10 g (0.036 mol) of epoxy alcohols **25** dissolved in 40 mL of CH_2Cl_2 was added dropwise over 20 min, followed by stirring for an additional 1.5 h. Isopropyl alcohol (8 mL) was added and the reaction mixture was stirred 5 min followed by concentration in vacuo at 25 °C. The crude residue was triturated with five 100-mL portions of boiling ether followed by in vacuo filtration of the extracts through Celite. The residue from the ether solution was triturated in the same manner with five 100-mL portions of petroleum ether. The crude residue was distilled (Kugelrohr) to afford 5.52 g (91%) of epoxy ketones 26: bp 90–120 °C (1 μm); IR (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.83 (1 H, m, lowest field signal, epoxide H).

Anal. ($C_{10}H_{16}O_2$): C, H.

Cyclopropyl Keto Alcohols 27a (syn) and 27b (anti). Potassium, 1.40 g (0.036 mol), was dissolved in 100 mL of dry *tert*-butyl alcohol (CaH_2) under N_2. To the stirred solution maintained at 25 °C was added dropwise over a period of 30 min 5.50 g (0.033 mol) of epoxy ketones **26** dissolved in 40 mL of dry *tert*-butyl alcohol. After the addition had been completed, the yellow solution was stirred for an additional 1.25 h, and then poured into an equal volume of saturated brine. The mixture was extracted with four 50-mL portions of ethyl acetate, dried, filtered, concentrated, and distilled [Kugelrohr, bp 90–120 °C (6 μm)] to provide 4.55 g of keto alcohols. The distillate was subjected to medium pressure chromatography (50–100 psi, 20 × 1 in. column of E. Merck Silica Gel 60H, EtAc solvent, 3 mL/min, 6 mL/fraction) providing 2.31 g (42%) of syn keto alcohol **27a**, 710 mg (13%) of a mixture (~1:1) of **27a** and **27b**, and 890 mg (16%) of anti keto alcohol **27b**.

Keto alcohol **27a**: IR (CCl_4) 3600–3200 and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3 H, s), 1.17 (3 H, d, J = 6 Hz), 3.89 (2 H, m), and 3.22 (1 H, br s, shifts on dilution).

Anal. ($C_{10}H_{16}O_2$) (VPC): C, H.

Keto alcohol **27b**: IR (CCl_4) 3600–3130 and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (3 H, d, J = 6 Hz), 1.18 (3 H, s), and 3.69 (2 H, m).

Anal. ($C_{10}H_{16}O_2$) (VPC): C, H.

Syn Keto Aldehyde 27c. To a solution of 919 mg (5.47 mmol) of syn keto alcohol in 450 mL of dry benzene was added 11.35 g of air-dried MnO_2[55] and the mixture was stirred at 25 °C for 25 h. The reaction mixture was filtered in vacuo through a bed of Celite and washed with four 15-mL portions of warm $CHCl_3$. The combined filtrates were evaporated in vacuo and distilled to give 795 mg (88%) of keto aldehyde **27c**:[57] bp 75–78 °C (4 μm, Kugelrohr); IR ($CHCl_3$) 2750 and 1705 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 6 Hz), 1.20 (3 H, s), 1.40–2.60 (7 H, m), and 9.70 (3 H, d, J = 3 Hz).

Anti Keto Aldehyde 27d. In the manner described for the preparation of the syn keto aldehyde **27c**, 484 mg (2.88 mmol) of anti keto alcohol provided 396 mg (83%) of anti keto aldehyde **27d**: bp 75–80 °C (5 μm, Kugelrohr); IR ($CHCl_3$) 2755 and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.40–2.39 (5 H, m), 2.47 (1 H, d, J = 4.5 Hz), 2.84 (1 H, t, J = 4.5 Hz), and 9.46 (1 H, d, J = 4.5 Hz).

Anal. ($C_{10}H_{14}O_2$): C, H.

***syn*-Cyclopropylacrylic Ester 27e.** To a stirred solution of 1.73 g (0.0104 mol) of syn keto aldehyde **27c** in 150 mL of CH_2Cl_2 maintained under N_2 at room temperature was added dropwise a solution of carbomethoxymethylenetriphenylphosphorane[58] in 50 mL of CH_2Cl_2 over a period of 30 min. After 13 h, the solvent was removed in vacuo at 25 °C. The residue was triturated with ether and allowed to stand in the cold for several hours. The crystalline triphenylphosphine oxide was filtered in vacuo and discarded. The concentrated residue was chromatographed on silica gel (45 g) providing 1.90 g (82%) of syn acrylic ester **27e** from the benzene–15% ether/benzene eluent. The material crystallized on standing and was recrystallized from ether–pentane: mp 52.5–53 °C; bp 80–85 °C (5 μm; Kugelrohr); IR ($CHCl_3$) 1715 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.17 (3 H, d, J = 7 Hz), 3.64 (3 H, s), 5.89 (1 H, d, J = 14.5 Hz), and 6.76 (1 H, dd, J = 14.5 and 8 Hz).

Anal. ($C_{13}H_{18}O_3$): C, H.

***anti*-Cyclopropylacrylic Ester 27f.** In the manner described above, 933 mg (5.62 mmol) of keto aldehyde **27d** was converted to 666 mg (53%) of ester **27f**: mp 93–94.5 °C (ether–pentane); IR ($CHCl_3$) 1715 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7 Hz), 1.19 (3 H, s), 2.60 (1 H, dd, J = 9 and 4 Hz), 3.67 (3 H, s), 5.90 (1 H, d, J = 15 Hz), and 6.59 (1 H, dd, J = 15 and 9 Hz).

Anal. ($C_{13}H_{18}O_3$): C, H.

***syn*-Cyclopropyl Keto Alcohol 32c.** A stirred mixture of 1.54 g (6.9 mmol) of syn acrylic ester **27e**, 25 mg (0.13 mmol) of *p*-toluenesulfonic acid, and 1.30 g (21.0 mmol) of ethylene glycol in 395 mL of anhydrous benzene (azeotrope) was refluxed utilizing a direct return (nonsyphon) Soxhlet extractor containing ~10–15 g of Linde 4A molecular sieves. After 75 min of refluxing the solution, the reaction mixture contained ~85% of the desired ketal plus starting material and rearranged ketal.[46] The reaction mixture was cooled to 25 °C, treated with 5 drops of triethylamine, and poured onto ~50 mL of a vigorously stirred solution of cold 2% NaOH. The layers were separated. The organic phases were washed twice with cold 2% NaOH and the combined basic extracts backwashed with ether. The combined organic solutions were dried, filtered, and concentrated in vacuo to provide 1.97 g of clear oil. Due to the lability of the ketal (decomposition upon distillation at 1 μm), the crude material was used without further purification. IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.64 (3 H, s), 3.87 (~4 H, s), 5.89 (1 H, d, J = 15 Hz), and 6.98 (1 H, dd, J = 15 and 10 Hz).

To a stirred mixture of 20 mL of anhydrous ether and 20 mL of dimethyl sulfide[59] under argon was added 3.32 g (0.017 mol) of cuprous iodide (Alfa-Ventron) followed by cooling to −78 °C in a dry ice–acetone bath. A solution of ethereal 2-lithiopropene (30 mL of 0.9 M and 10 mL of 0.8 M, i.e., 35 mmol) (vide supra) was added via the syringe-serum cap technique at such a rate that the temperature did not exceed −33 °C. After stirring the solution for 45 min, the crude ketal (1.97 g) in 35 mL of ether was added dropwise over 5–10 min. The mixture was stirred an additional 1 h below −60 °C and then allowed to come to 25 °C over 4 h. The reaction mixture was poured onto an equal volume of saturated NH_4Cl solution and stirred 30 min. The mixture was filtered in vacuo through a pad of Celite and the aqueous phase extracted thoroughly with ether. The combined organic extracts were washed with saturated brine, dried, filtered, and concentrated. The residue was triturated with pentane, filtered (to remove trace amounts of copper salts), and concentrated to give 2.55 g of crude ketal **32b** as a dark oil: NMR ($CDCl_3$) δ 0.99 (3 H, d, J = 6 Hz), 1.02 (3 H, s), 1.75 (3 H, s), 3.64 (3 H, s), 3.95 (4 H, br s), and 4.83 (2 H, s).

To a stirred suspension of 380 mg (10.0 mmol) of lithium aluminum hydride in 50 mL of ether was added dropwise 2.55 g of the crude ketal ester dissolved in 35 mL of ether followed by stirring of the mixture at 25 °C overnight. The reaction mixture was cautiously decomposed with saturated aqueous Na_2SO_4 solution. The white granular mass was dried with anhydrous Na_2SO_4, filtered, and concentrated.

The residue (2.18 g) was stirred for 45 min in 80 mL of 1:1 THF–3% aqueous HCl. The reaction mixture was diluted with water and extracted thoroughly with ether. The combined extracts were washed with saturated brine, dried, filtered, and concentrated to afford 1.96 g of dark oil. The residue was subjected to medium pressure chromatography (vide supra, 3:1 ethyl acetate–hexane), providing 717 mg of keto alcohol **32c** (44% overall): IR (CCl_4) 3650–3390 and 1678 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (2 H, t, J = 6 Hz) and 4.80 (2 H, br s); MS m/e (70 eV) ($C_{15}H_{24}O_2$) 236.17775 (calcd), 236.18086 (obsd).

***anti*-Cyclopropyl Keto Alcohol 35.** Employing the reaction sequence used in the previous experiment, 438 mg (1.97 mmol) of *anti*-cyclopropylacrylic ester was converted to 522 mg (100%) of crude ketal: NMR ($CDCl_3$) δ 3.70 (3 H, s), 3.93 (4 H, s), 5.98 (1 H, d, J = 16 Hz), and 6.80 (1 H, d, d, J = 16 and 9 Hz).

Cuprate adduct: NMR ($CDCl_3$) δ 1.70 (3 H, s), 3.57 (3 H, s), 3.87 (4 H, br s), and 4.65 (2 H, s).

Keto alcohol **35**: 74% overall; IR (CCl_4) 3640–3350 and 1679 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6 Hz), 1.13 (3 H, s), 1.70 (3 H, s), 3.60 (1 H, t, J = 7 Hz), and 4.78 (2 H, br s); MS m/e 70 eV ($C_{15}H_{24}O_2$) 236.17775 (calcd), 236.17970 (obsd).

Keto Alcohol 33a. Into a flask capped with a dry ice condenser was distilled 50 mL of liquid ammonia (from Na metal). The flask was cooled to −78 °C followed by the addition of 252 mg (36 mmol) of lithium wire cut into small pieces. After stirring the mixture for 1 h, 717 mg (3.0 mmol) of *syn*-cyclopropyl keto alcohol **32c** dissolved in 25 mL of anhydrous ether was added dropwise over 15 min, followed by stirring for an additional 75 min. The cold bath was removed and solid NH_4Cl was added cautiously to the reaction mixture until the blue color had discharged. The solvent was allowed to evaporate overnight. The residue was dissolved in H_2O and extracted thoroughly with ether. The combined organic extracts were washed with saturated brine, dried, filtered, concentrated, and distilled to give 628 mg (88%) of keto alcohol **33a**: bp <165 °C (2 μm, Kugelrohr); IR 3650–

3200 and 1709 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (3 H, s), 0.88 (3 H, d, J = 6 Hz), 1.68 (3 H, s), 3.29 (1 H, br s, OH), 3.50 (1 H, t, J = 6 Hz), and 4.77 (2 H, br s); MS m/e 70 eV ($C_{15}H_{26}O_2$) 238.19340 (calcd), 238.19280 (obsd).

Keto Alcohols 33. *anti*-Cyclopropyl keto alcohol **35** (554 mg, 2.35 mmol) gave 420 mg (75%) of keto alcohols 33: bp < 165 °C (2 μm, Kugelrohr); IR (CCl_4) 3650–3200 and 1709 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (3 H, s), 0.91 (3 H, d, J = 6 Hz), 1.65 (~3 H, s), 3.57 (1 H, t, J = 6 Hz), and 4.81 (2 H, m); MS m/e 70 eV ($C_{15}H_{26}O_2$) 238.19340 (calcd), 238.19396 (obsd).

Enone 18b. To a stirred solution of 2.50 g (32 mmol) of pyridine and 30 mL of CH_2Cl_2 maintained at 0 °C was added 1.58 g (15.8 mmol) of chromium trioxide. After stirring the mixture for 45 min at 25 °C, 628 mg (2.6 mmol) of keto alcohol **33a** in 20 mL of CH_2Cl_2 was added over 5 min, followed by stirring of the reaction mixture for 30 min. The reaction mixture was poured into 250 mL of ether and filtered (Celite) in vacuo. The combined filtrates were washed with ice cold 3% HCl, ice cold 1% NaOH, ice cold 3% HCl, and finally saturated brine. The ether solution was dried, filtered, and concentrated to give 555 mg (88%) of crude aldehyde **34a**: NMR ($CDCl_3$) δ 9.22 (t, J = 3 Hz).

The aldehyde was aldolized and dehydrated as described (vide supra). The crude dehydration product showed <2% [NMR, VPC (OV-1, 140 °C)] of the epimer **18a**. The material was purified twice by thick-layer chromatography (5% EtAc–C_6H_6) to give 104 mg[60] of pure enone **18b**: IR (CCl_4) 1688 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s), 0.93 (3 H, d, J = 6 Hz), 1.75 (3 H, s), 4.73 (2 H, br s), and 6.18 (1 H, m).

Anal. ($C_{15}H_{22}O$): C, H.

Enones 18a and 18b. In the manner described (vide supra), 420 mg (1.8 mmol) of keto alcohols 33 were converted to 147 mg of enones **18a** and **18b**.

Keto aldehydes 34: NMR ($CDCl_3$) δ 9.24 (t, J = 3 Hz).

Enones **18a** and **18b**: IR (CCl_4) 1685 cm^{-1}; NMR ($CDCl_3$, normal amplitude) δ 0.96 (6 H, m), 1.75 (3 H, s), 4.75 (2 H, br s), and 6.40 (1 H, m). A high-amplitude spectrum of the region δ 6–7 showed signals at both δ 6.40 and 6.18 in an 85/15 ratio, respectively. This ratio was confirmed by VPC integration (OV-1, 140 °C).

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Registry No.—**1,** 53797-64-1; **8a,** 61847-10-7; **8b,** 61913-85-7; **9a,** 61847-11-8; **9b,** 61847-12-9; **11,** 53768-14-2; **13,** 61847-13-0; **14a,** 53768-21-1; **14b,** 53768-22-2; *E*-**15a,** 53768-23-3; *Z*-**15a,** 61913-86-8; **15b,** 53768-24-4; **15c,** 61913-87-9; **15d,** 61847-14-1; **16a,** 61847-15-2; **16b** isomer 1, 61847-16-3; **16b** isomer 2, 61913-88-0; **17a** isomer 1, 61847-17-4; **17a** isomer 2, 61913-89-1; **17b** isomer 1, 53768-13-1; **17b** isomer 2, 53834-80-3; **18a,** 53802-60-1; **18b,** 53768-26-6; **19,** 53768-28-8; **20,** 53768-27-7; **21,** 61847-18-5; **22,** 61847-19-6; **23,** 53797-63-0; **24** isomer 1, 61847-20-9; **24** isomer 2, 61847-21-0; **25,** 61847-22-1; **26** isomer 1, 61847-23-2; **26** isomer 2, 61913-90-4; **27a,** 61847-24-3; **27b,** 61847-25-4; **27c,** 61847-26-5; **27d,** 61847-27-6; **27e,** 61847-28-7; **27f,** 61847-29-8; **28,** 61847-30-1; **30b** isomer 1, 61847-31-2; **30b** isomer 2, 61913-91-5; **31,** 61847-32-3; **32a,** 61847-33-4; **32b,** 61847-34-5; **32c,** 61847-35-6; **33a,** 61847-36-7; **33b,** 61913-92-6; **35c,** 61847-37-8; 3,4-dimethylcyclohexenone, 1123-09-7; allene, 463-49-0; *cis*-9 deoxo, 61847-38-9; *trans*-9 deoxo, 61847-39-0; *cis*-9 alcohol analogue, 61847-40-3; *trans*-9 alcohol analogue, 61847-41-4; *cis*-1,2-dimethylcyclohexanecarboxylic acid, 61847-42-5; *trans*-1,2-dimethylcyclohexanecarboxylic acid, 61847-43-6; *trans*-1,2-dimethylcyclohexylnitrile, 61847-44-7; *cis*-1,2-dimethylcyclohexylnitrile, 61847-45-8; *cis*-1,2-dimethylcyclohexanecarboxaldehyde, 61847-46-9; *trans*-1,2-dimethylcyclohexanecarboxaldehyde, 61847-47-0; 2-methyl-2-butene 513-35-9; ethylene glycol, 107-21-1; α-carbomethoxyethylidenetriphenylphosphorane, 40467-01-4; ethyl diethylphosphonoacetate, 867-13-0; ethyl orthoacetate, 78-39-7; 2-bromopropene, 557-93-7; *m*-chloroperbenzoic acid, 937-14-4; carbomethoxymethylenetriphenylphosphorane, 2605-67-6.

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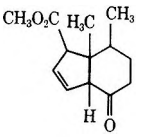
(46) The syn ester **27e** is stable in refluxing benzene, with or without *p*-TsOH. In the presence of ethylene glycol, a second peak (VPC) slowly appears. Hydrolysis of the ketalization mixture provides **27e** and a product which was identical with a material isolated from hydrolysis of a ketalization which had proceeded for an extended period of time. This substance's NMR spectrum was consistent with i, arising by an acid-catalyzed vinylcyclopropane rearrangement due to the steric compression of the ketal group.



i

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Notes

Methyldialkylcyanodiazenecarboxylates as Intermediates for Transforming Aliphatic Ketones into Nitriles

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Several years ago we described[3] a method for converting aliphatic ketones into nitriles by the base-induced decomposition of methyl dialkylcyanodiazenecarboxylates. The method permits the in situ methylation and carbomethoxylation of the intermediate nitrile anions, thereby constituting a method for geminal substitution at the α carbonyl carbon.[4] This Note provides the experimental details for this reaction. The diazenes **1b–4b** were readily prepared as outlined in Scheme I. Generation of hydrogen cyanide in situ (KCN–NH_4Cl) gave somewhat lower yields than liquid HCN, due to water solubility of the products.

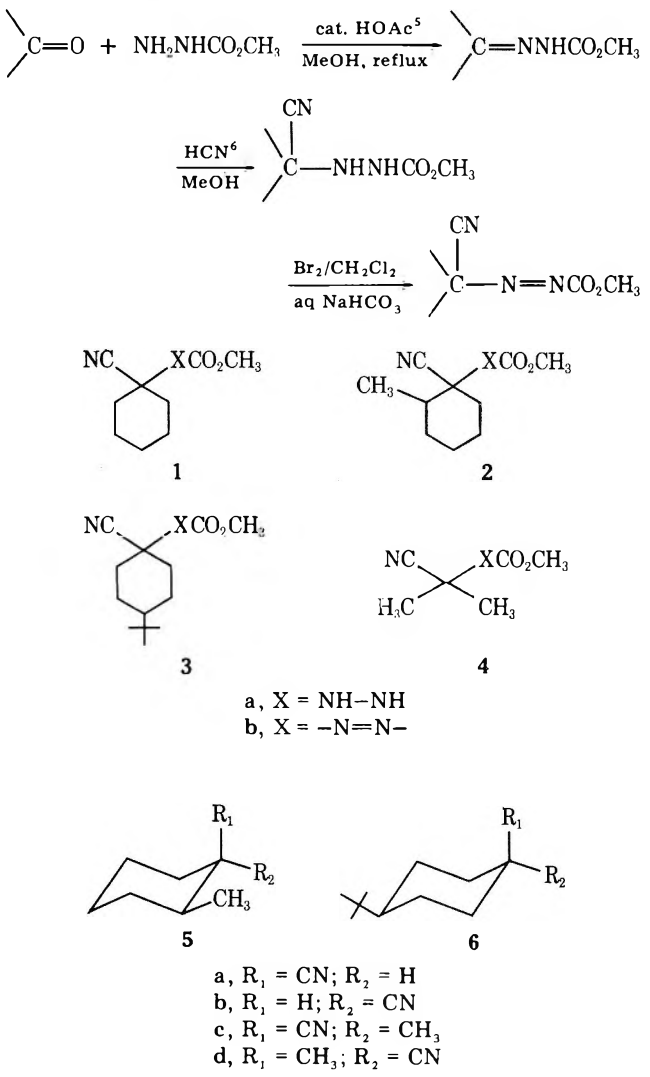
The decomposition of diazene **1b** with catalytic NaOMe in MeOH at 0 °C provided cyclohexylnitrile in 94% yield (VPC). When MeOH-d_1 was employed, cyclohexylnitrile-d_1 was obtained. The cleavage with methoxide also undergoes a degenerate methoxide exchange with the substrate. Evidence for this process was obtained by employing a two-phase system of ether and water, the yellow diazene being soluble in the former phase. When dilute aqueous NaOH was added slowly to the mixture at 0 °C, the aqueous phase turned yellow (diazenecarboxylate salt) as gas was evolved from the same phase. When gas evolution had ceased, the reaction mixture was colorless.

Diazene **2b** provided approximately an equal mixture of *cis*-(**5a**) and *trans*-2-methylcyclohexylnitrile (**5b**), while the 4-*tert*-butyldiazene **3b** gave rise to two nitriles in a ratio of 58/42 by VPC analysis. Rickborn and Jensen[7a] have shown that the equilibrium (*t*-BuOK/*t*-BuOH) of 4-*tert*-butylcyclohexylnitrile favors the equatorial nitrile **6b** over the axial isomer **6a** (**6b/6a** = 56/44). Subjection of the mixture to these conditions provides a thermodynamic mixture, the major component now becoming the minor component. Thus, the catalytic decomposition provides a kinetic mixture, wherein the axial nitrile **6a** predominates.

In order to permit alkylation of the nitrile anion, it was necessary to perform the reaction with stoichiometric quantities of methoxide and to employ an aprotic solvent. Anhydrous lithium methoxide was prepared in situ from anhydrous methanol and butyllithium (hexane) or methyllithium (ether) in dimethoxyethane (DME). When the diazene in the presence of an excess of methyl iodide was added dropwise at 0 °C to the base, the yellow diazene color was discharged and gas evolution occurred providing from diazene **1b** an 84% yield of products consisting of 1-methylcyclohexylnitrile 77%) and 1-carbomethoxycyclohexylnitrile (13%). This method of addition of the methyl iodide is necessary, since, if the diazene is added first and then the methyl iodide, upwards of 70% of the reaction mixture consists of 1-carbomethoxycyclohexylnitrile. This arises from the nitrile anion reacting with generated dimethyl carbonate or unreacted diazene. The concomitant addition procedure allows the alkylation to favorably compete with the acylation. An efficient procedure for the preparation of 1-carbomethoxycyclohexylnitrile was achieved by adding the diazene to the $LiOCH_3$/DME containing excess dimethyl carbonate.

The in situ methylation of the nitrile anion from diazene **2b** provided a diastereomeric mixture (**5c/5d** = 73/27) of methylated nitriles (63%) and a diastereomeric mixture of carbomethoxylated nitriles (25%). The identity of the minor methylated nitrile was confirmed by synthesis from the Diels–Alder adduct of tiglic acid and butadiene.[4b,7] A similar decomposition of diazene **3b** provided 1-methyl-4-*tert*-butylcyclohexylnitrile as a mixture of diastereomers (**6c/6d** = 76/24) in 70% yield along with 23% of carbomethoxylated product. House and Bare[8] have obtained a similar ratio (71/29)

Scheme I



by treating 4-*tert*-butylcyclohexylnitrile with lithium diethylamide followed by methyl iodide.

Since methylation is among the least sterically demanding of alkylation procedures, and in view of the fact that approximately 25% of carbomethoxylated product is obtained in the in situ process, it is more efficient to generate the nitriles by the protic sequence followed by alkylation using dialkylamide bases.[8]

Experimental Section

Vapor-phase chromatography (VPC) analyses were determined on an Aerograph A-90-P or Varian Aerograph Model 90-P instrument employing a 20 ft × ⅜ in. 20% SE-30 on Chromosorb W (45/60) column. Cyclohexylnitrile, cyclohexanone, or biphenyl were used as internal standards. Infrared spectra (IR) were determined on a Perkin-Elmer Model 421 or 337 spectrometer. Nuclear magnetic resonance spectra (NMR) were recorded on a Jeolco Model JNM-MH-100 or Varian A-60A spectrometer using Me_4Si as an internal standard. Melting points were determined on a Fisher–Johns apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories or Atlantic Microlabs and are within 0.3% of the theoretical composition. Cyclohexanone, 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, methyl carbazate, *n*-butyllithium, and methyllithium were obtained commercially. Organic extracts were dried over anhydrous magnesium sulfate. Dimethoxyethane (DME) was distilled from sodium benzophenone ketyl and methanol from $Mg(OCH_3)_2$.

Hydrazine 1a (via liquid HCN). To a solution of 4.5 g (50.0 mmol) of methyl carbazate in 10 mL of methanol containing a drop of acetic acid was added 4.9 g (50.0 mmol) of cyclohexanone. The solution was refluxed for 30 min, concentrated in vacuo, taken up in ether, and dried. Filtration and concentration of the solution gave light yellow oil which was dissolved in 10 mL of methanol, cooled to 0 °C with stirring, and treated with 6 mL (~150 mmol) of liquid hydrogen cyanide[9] (HOOD!) at such a rate that the temperature remained below 10 °C. After 15 min a heavy, white precipitate formed, requiring the addition of 10 mL of methanol to facilitate stirring. After 30 min, the mixture was filtered and washed with methanol to afford 7.0 g of white crystalline solid. Concentration of the mother liquors provided an additional 2.5 g (97.5%). Recrystallization (methanol/pentane) provided a sample of hydrazine **1a**: mp 135–136 °C IR ($CHCl_3$) 3600–3200, 2235, and 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.82 (3 H, s), 4.46 (1 H, br s), and 6.82 (1 H, br s).

Anal. ($C_9H_{15}N_3O_2$): C, H, N.

Hydrazine 2a: 90% yield; mp 138 °C (methanol/pentane); IR ($CHCl_3$) 3700–3250, 2235, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3 H, d, J = 6 Hz), 3.82 (2 H, s), 4.62 (1 H, br d, J = 4 Hz), and 6.76 (1 H, br d, J = 4 Hz).

Anal. ($C_{10}H_{17}N_3O_2$): C, H, N.

Hydrazine 3a: 90% yield; mp 132–133.5 °C (methanol/pentane); IR ($CHCl_3$) 3700–3225, 2230, and 1730 cm^{-}; NMR ($CDCl_3$) δ 0.90 (9 H, s), 3.80 (3 H, s), 4.54 (1 H, br s), and 6.92 (br s).

Anal. ($C_{13}H_{23}N_3O_2$): C, H, N.

Hydrazine 4a: 98% yield; mp 99.5–101 °C (methanol/pentane); IR ($CHCl_3$) 3700–3200, 2230, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (6 H, s), 3.80 (3 H, s), 4.46 (1 H, br d, J = 4 Hz), and 6.80 (1 H, br s).

Anal. ($C_6H_{11}N_3O_2$): C, H, N.

Hydrazine 1a (via in situ generation of HCN). To 0.1 mol of the carbazone of cyclohexanone (vide supra) was added a solution of 15.5 g (0.3 mol) of ammonium chloride and 16 g (0.3 mmol) of potassium cyanide in 75 mL of water and 50 mL of methanol. After stirring the mixture at room temperature for 18 h, the solution was diluted with 100 mL of water and thoroughly extracted with CH_2Cl_2. After drying, concentration, and crystallization (MeOH/pentane), hydrazine **1a** was obtained in 60% yield.

Diazene 1b. To a vigorously stirred mixture of 11.7 g (0.06 mol) of hydrazine **1a** in 100 mL of CH_2Cl_2 and 15.1 g (0.18 mol) of $NaHCO_3$ in 100 mL of H_2O was added dropwise 24 mL (67 mmol) of a 2.8 M Br_2/CH_2Cl_2 solution over 10 min at room temperature. After the addition had been completed, the mixture developed a persistent orange-red color (+ KI-starch). The excess bromine was discharged by the addition of small portions of solid Na_2SO_3 to the reaction mixture. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (two 50-mL portions). The combined organic fractions were washed with H_2O (50 mL), dried, filtered, and concentrated. The residue was distilled to provide 11.0 g (95%) of diazene **1b** as a bright yellow liquid: bp 115 °C (1.3 mm); IR (CCl_4) 1785 cm^{-1}; NMR ($CDCl_3$) δ 3.98 (3 H, s).

Anal. ($C_9H_{13}N_3O_2$): C, H, N.

Diazene 2b: 96% yield; bp 103 °C (0.4 mm); IR (CCl_4) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (3 H, d, J = 7 Hz), and 4.20 (3 H, s).

Anal. ($C_{10}H_{15}N_3O_2$): C, H, N.

Diazene 3b: 96% yield; mp 89.5–90.5 °C (ether/pentane); IR (CCl_4) 2245 and 1775 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (9 H, s) and 4.11 (3 H, s).

Anal. ($C_{13}H_{21}N_3O_2$): C, H, N.

Protic Decomposition of Diazene 1b. To a solution of 540 mg (10 mmol) of $NaOCH_3$ in 5 mL of CH_3OH maintained at 0 °C was added dropwise 3.9 g (20 mmol) of diazene **1b** in 10 mL of ether/methanol (1/1). The addition proceeded with vigorous gas evolution and required approximately 30 min for completion, during which time the temperature was maintained between 0 and 10 °C. When gas evolution had ceased, the solution was allowed to warm to room temperature and was diluted with water (10 mL). The mixture was thoroughly extracted with ether, dried, filtered, concentrated, and distilled to provide a 94% yield of cyclohexylnitrile (compared with an authentic sample).

Protic Decomposition of Diazene 3b. In the manner described *cis*- (**6a**) and *trans*-4-*tert*-butylcyclohexylnitrile (**6b**) were obtained in 96% yield (VPC). Samples collected via preparative GLC gave: **6a**, mp 57 °C (lit.[7b] 56.3–57.3 °C, IR (CCl_4) 2240 cm^{-1}, NMR ($CDCl_3$) δ 0.89 (9 H, s) and 2.96 (1 H, m); **6b**, mp 33–34 °C (lit.[7b] 33.4–34.7 °C), IR (CCl_4) 2240 cm^{-1}, NMR ($CDCl_3$) δ 0.85 (9 H, s).

Aprotic Decomposition of Diazene 1a (methylation). To solution of 1.75 mL (45 mmol) of dry methanol in 20 mL of dry DME containing a trace of triphenylmethane maintained under N_2 at 0 °C was added 20 mL (46 mmol) of 2.3 M BuLi in hexane until a pink color persisted. To the reaction mixture was added a solution of 1.95 g (10.0 mmol) of diazene **1b** and 8 mL (120 mmol) of methyl iodide in 20 mL of dry DME over a period of 1 h at 3–10 °C. After the addition was complete, the reaction mixture was stirred at 25 °C for 1 h, then diluted with 40 mL of H_2O and thoroughly extracted with ether, dried,

and concentrated. Analysis (VPC) of the residue indicated two products formed in 84% yield. The major material (86%) was identical (NMR, VPC collected) with 1-methylcyclohexylnitrile prepared by the procedure of House,[8] while the minor component was identical with 1-carbomethoxycyclohexynitrile prepared from methyl 2-cyano-6-heptenoate.[10]

Aprotic Decomposition of Diazene 2b. In the manner described (vide supra) VPC analysis indicated an overall yield of 90% consisting of *trans*-1,2-dimethylcyclohexylnitrile (**5c**, 46%) [IR (CCl_4) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (3 H, d, J = 8 Hz), 1.34 (3 H, s), and 0.95–2.14 (9 H, m)], *cis*-1,2-dimethylcyclohexylnitrile (**5d**, 17%), identical with a sample prepared from butadiene and tiglic acid,[4b] diastereomeric 2-methyl-1-carbomethoxycyclohexylnitrile (25%) [IR (CCl_4) 2245 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (3 H, d, J = 6 Hz), 1.15–2.37 (9 H, m), and 3.90 (3 H, s)], and diastereomeric 2-methylcyclohexylnitrile (≤2% **5a** and **5b**), identical with material from the protic decomposition.

Aprotic Decomposition of Diazene 3b. As described (vide supra), a combined yield of 95% was obtained consisting of *trans*-1-methyl-4-*tert*-butylcyclohexylnitrile (53%, **6c**), *cis*-1-methyl-4-*tert*-butylcyclohexylnitrile (17%, **6d**),[7] diastereomeric 1-carbomethoxy-4-*tert*-butylcyclohexylnitrile (23%) [IR (CCl_4) 2240 and 1740 cm^{-1}; NMR (CCl_4) δ 0.91 (9 H, s), 0.82–2.32 (9 H, m), and 3.91 (3 H, s)], and diastereomeric 4-*tert*-butylcyclohexylnitrile (≤1%, **6a** and **6b**), identical with material from the protic decomposition.

Carbomethoxylation of Diazene 1b. To a mixture of 45 mmol of lithium methoxide (vide supra) and 10.8 g (0.120 mol) of freshly distilled dimethyl carbonate maintained under N_2 at 0–5 °C was added dropwise over 25 min 1.95 g (10.0 mmol) of diazene **1b** in 15 mL of DME. After the addition was complete, the solution was allowed to warm to 25 °C, then diluted with 25 mL of H_2O and thoroughly extracted with ether, dried, filtered, and concentrated. The residue accounted for an 84% yield (VPC) consisting of cyclohexylnitrile (7%) and 1-carbomethoxycyclohexylnitrile (77%), both spectroscopically (IR and NMR) identical with authentic samples.

Acknowledgment. Financial support for this work was provided in part by the National Science Foundation (GP-11273), the National Cancer Institute, National Institutes of Health (CA-08869), and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1a**, 61827-29-0; **1b**, 33670-04-1; **2a**, 61827-30-3; **2b**, 33794-84-2; **3a**, 61827-31-4; **3b**, 33670-05-2; **4a**, 61827-32-5; **5a**, 25144-00-7; **5b**, 10479-61-5; **5c**, 61827-33-6; **5d**, 61827-34-7; **6a**, 15619-19-9; **6b**, 15619-18-8; **6c**, 15619-22-4; **6d**, 15619-20-2; methylcarbazate, 6294-89-9; cyclohexanone, 108-94-1; 2-methylcyclohexanone, 583-60-8; 4-*tert*-butylcyclohexanone, 98-53-3; acetone, 67-64-1; *trans*-1-carbomethoxy-4-*tert*-butylcyclohexylnitrite, 61827-35-8; *cis*-1-carbomethoxy-4-*tert*-butylcyclohexylnitrile, 61827-36-9; *trans*-2-methyl-1-carbomethoxycyclohexylnitrile, 61827-37-0; *cis*-2-methyl-1-carbomethoxycyclohexylnitrile, 61827-38-1.

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Rotational Energy Barriers in 1-(3,4,5-Trimethoxyphenyl)benz[*h*]imidazo[1,5-*a*]quinoline and Related Compounds

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During our synthetic investigations on certain benzimidazoquinoline and -isoquinoline systems,[2] it was noted that 1-aryl derivatives of benz[*h*]imidazo[1,5-*a*]quinoline gave rise to temperature-dependent NMR spectra. Hindered rotation of the aryl group about the aryl–C_1 bond would account for the observed phenomena.[3a-d] The temperature dependence of the NMR spectra of several of these compounds has now been studied in greater detail.

In the NMR spectrum of 1-(3,4,5-trimethoxyphenyl)-benz[*h*]imidazo[1,5-*a*]quinoline (**1**) at ambient temperature and above, the three methoxy groups appear as two singlets, a three-proton singlet at 3.79 ppm and a six-proton peak at 3.44 ppm (corresponding to the methoxy groups in the 3 and 5 positions) as shown in Figure 1.[4] The protons on the phenyl ring at the 2 and 6 positions appear as a singlet at 6.50 ppm. As the temperature is lowered the 3- and 5-methoxy groups give rise to two peaks which eventually attain chemical shifts of 2.76 and 4.13 ppm at the lowest temperature obtainable in the deuteriochloroform solvent, −67 °C. At this temperature the peak separation, $\Delta\nu$, is 124 Hz. Likewise, the two phenyl ring protons form two peaks, one at 5.49 ppm, the other buried in the aromatic envelope. Coalescence was observed to occur at −23 ± 2 °C for the peaks of the methoxy groups at the 3 and 5 positions.[5] Of the two sets of signals, those corresponding to the methoxy groups were used for the subsequent lineshape analysis.

Since $\Delta\nu$ in the absence of exchange is important both in the computer and manual calculations, it was desirable to determine whether or not the separation increased significantly at lower temperatures. A plot of $\Delta\nu$ vs. temperature approaches 125 Hz at low temperature, and $\Delta\nu$ was found to be 124.7 Hz at −79 °C in dichloromethane solution. It thus appears that $\Delta\nu$ was within 1 or 2 Hz of its maximum value and an error of a few hertz would have a negligible effect upon the calculations. To avoid residual broadening errors due to rotation of the methoxy groups, the signal at 3.79 ppm was used as a resolution standard. This was found to broaden somewhat as the temperature was lowered when checked against dichloromethane.

A Dreiding model of **1** indicates that complete rotation of the aryl group about the aryl–C_1 bond is not allowed. Consequently, in the extreme allowed conformations the 2 and 3 and then the 4 and 5 positions are alternately above and then tilted away from the π-electron cloud of the benz[*h*]quinoline ring system, as in the hexahelicene-like conformations **1a** and **1b**. The model suggests that the benz[*h*]imidazo[1,5-*a*]quinoline ring system is planar, in which case **1a** and **1b** are enantiomeric. Thus the 3- and 5-methoxy groups should give rise to two NMR signals at low temperature. A similar argument can

Table I

Compd	Groups	T_c, °C	$\Delta\nu$, Hz	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal/mol	Method[a]
1	3,5-CH_3O	−23 ± 2	124	10.9 ± 0.3	10.4 ± 0.3	−5.6 ± 1.2	11.8 ± 0.4	1
1	3,5-CH_3O	−23 ± 2	124	11.1 ± 0.3	10.6 ± 0.3	−4.3 ± 1.1	11.7 ± 0.4	2
1	3,5-CH_3O	−23 ± 2	124				11.8 ± 0.1	3
2	3,5-CH_3O	−31 ± 2	89.5	10.6 ± 0.3	10.2 ± 0.3	−5.5 ± 1.1	11.5 ± 0.4	2
2	3,5-CH_3O	−31 ± 2	89.5				11.5 ± 0.1	3
3	2,6-H	−29 ± 3	176				11.3 ± 0.1	3

[a] Methods used in data workup: (1) computer line-shape analysis; (2) equations in Experimental Section; (3) Gutowsky–Holm approximation and Eyring equation[3d] at T_c.

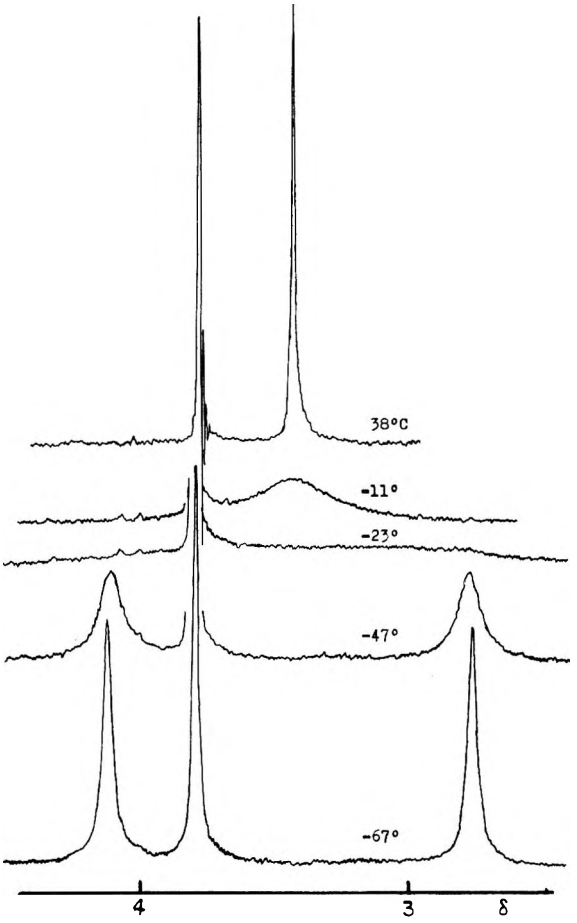
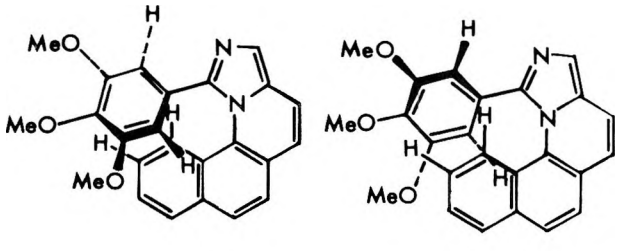


Figure 1. Temperature effects on the NMR spectrum of the methoxy groups of 1.



1a 1b

be made for the 2 and 6 protons. A nonplanar benz[*h*]imidazo[1,5-*a*]quinoline system would produce diastereomeric pairs, which could exhibit up to four NMR signals for the 3- and 5-methoxy groups at low temperature. The observed spectra support the planarity indicated by the model.

The rotational energy barrier in 1 was determined by a computer line-shape analysis using a program by D'Agostino[7] and Macomber[8] (similar to DNMR2).[9] Spectra for the methoxy groups were calculated at various lifetimes and matched to the observed peaks by comparison of the widths at half-height. The natural line width at a given temperature was taken to be that of the 3.79-ppm signal. The matched spectra covered a temperature range of 73 °C. Rate constants were calculated from the appropriate lifetimes and an Arrhenius plot (ln k vs. $1/T$) was constructed as indicated in Figure 2. The activation energy, E_a, was determined to be 10.9 ± 0.3 kcal/mol. The values for the entropy of activation, $\Delta S^{\ddagger}$, and the free energy of activation, $\Delta G^{\ddagger}$, from the appropriate equations,[3b] were −5.6 ± 1.2 eu and 11.8 ± 0.4 kcal/mol, respectively.

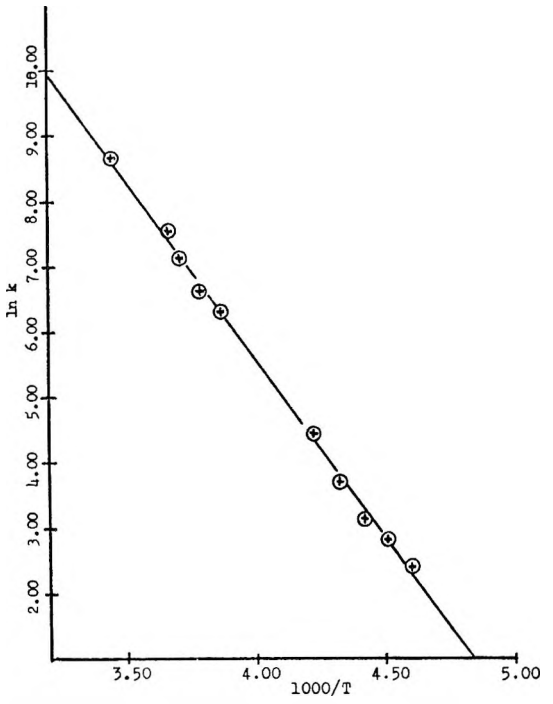


Figure 2. Arrhenius plot for the enantiomerization of 1, computer line-shape analysis.

These results compare favorably with data obtained by less rigorous methods using (a) an Arrhenius plot (see Figure 3) of data derived through manual calculation of lifetimes from approximation equations (Experimental Section) and (b) the Gutowsky–Holm approximation[3c,6] and the Eyring equation[3d] at the coalescence temperature, T_c.[3b] Data derived by the three methods are summarized in Table I.

The good agreement of the data for 1 obtained by the different methods encouraged us to compare 1 with some similar compounds for which computer-derived data were not readily obtainable. An Arrhenius plot for 1-(3,5-dimethoxyphenyl)-benz[*h*]imidazo[1,5-*a*]quinoline (2) over a range of 98 °C is shown in Figure 4. The activation energy was determined to be 10.6 ± 0.3 kcal/mol and $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ were −5.5 ± 1.1 eu and 11.5 ± 0.4 kcal/mol, respectively. Likewise, for 1-phen-

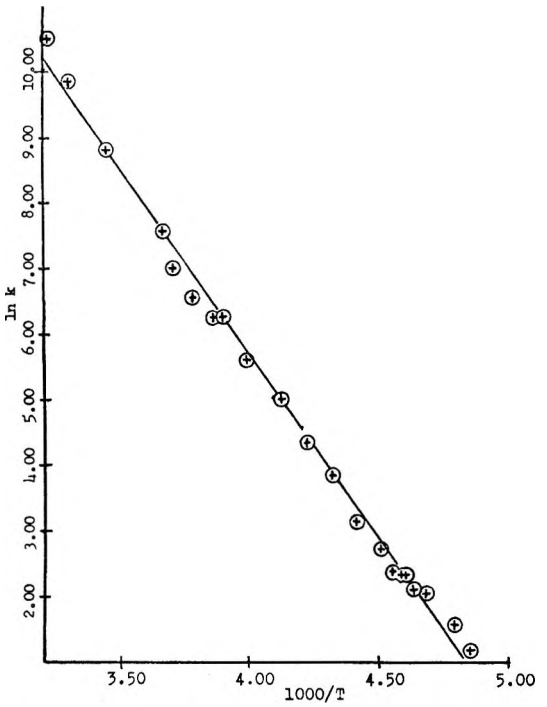


Figure 3. Arrhenius plot for the enantiomerization of **1**, manual calculations.

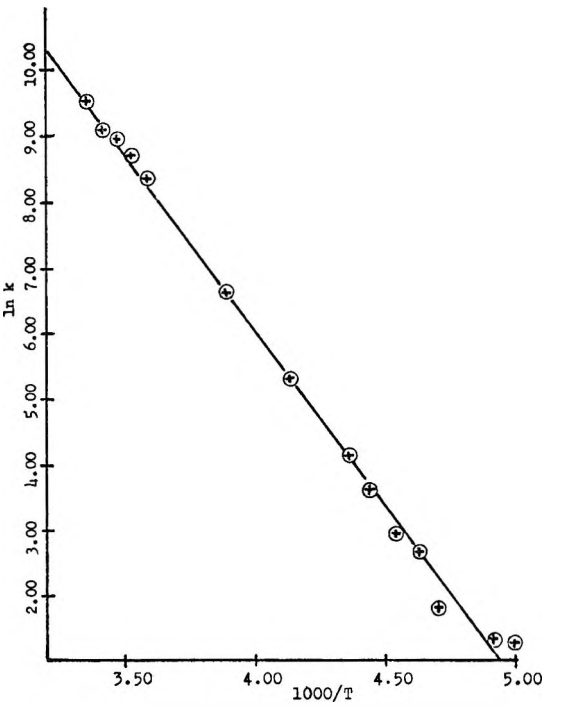
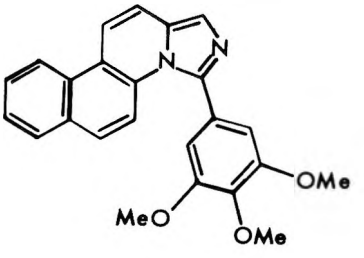


Figure 4. Arrhenius plot for the enantiomerization of **2**, manual calculations.

ylbenz[*h*]imidazo[1,5-*a*]quinoline (**3**), $\Delta G^{\ddagger}$ was determined to be 11.3 ± 0.1 kcal/mol from the Gutowsky–Holm approximation.[6,9] Sample spectral data for **3** are given in Figure 5. In contrast, the spectrum of 1-(3,4,5-trimethoxyphenyl)-benz[*f*]imidazo[1,5-*a*]quinoline (**4**) did not show significant



4

broadening of the signal corresponding to the 3- and 5-methoxy groups until −65 °C in deuteriochloroform, indicating a much lower $\Delta G^{\ddagger}$ for this compound.

Comparison of the data for **1**, **2**, and **3** summarized in Table I indicates that the π-overlap of the phenyl ring with the benz[*h*]quinoline ring system must be substantial in the most stable conformation of these compounds, but that complete planarity is sterically precluded. It is likely that, as suggested by the model, the aryl substituent cannot undergo 360° rotation but rather changes conformations only by a rocking motion. This is especially apparent from the data for **3** where removal of the methoxy groups from the phenyl ring caused only a slight decrease in the free energy of activation. The transition state for this process is that conformation in which the phenyl ring is perpendicular to the tetracyclic portion of the molecule.

Experimental Section

Compounds **1**, **3** and **4** were prepared as described previously.[2] Compound **2**, 1-(3,5-dimethoxyphenyl)benz[*h*]imidazo[1,5-*a*]quinoline, mp 152–154 °C (2-propanol) [Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.39): C, 77.95; H, 5.12; N, 7.91. Found: C, 77.79; H, 5.17; N, 7.65] was obtained through $POCl_3$-induced ring closure of *N*-(2-benz[*h*]-quinolylmethyl)-3,5-dimethoxybenzamide, mp 150–152 °C (aqueous EtOH) [Anal. Calcd for $C_{23}H_{20}N_2O_3$ (372.41): C, 74.17; H, 5.41; N, 7.52. Found: C, 74.17; H, 5.55; N, 7.44].

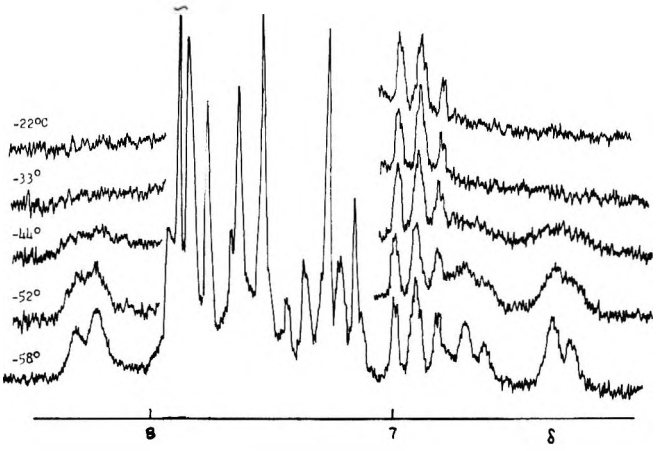


Figure 5. Temperature effects on the NMR spectrum of **3**.

Analytically pure sample was dissolved in $CDCl_3$ or CD_3COCD_3 (**2** only), concentration ca. 5–10%, and filtered into a precision NMR tube. NMR spectra were recorded on a Bruker HFX-10 90-MHz spectrometer equipped with a temperature controller. Frequency sweep was employed using 2–5% Me_4Si as an internal standard and chemical shifts are reported in δ units. A sweep width of 10 Hz/cm was normally employed. For **1**, smaller sweep widths were also used at the low and high temperature extremes. Power levels were carefully adjusted to avoid saturation effects. The probe temperatures was calibrated using methanol as a thermometer liquid and the van Geet equation modified for use at 90 MHz:

$$T\,(\mathrm{K}) = 406.0 - 0.367\Delta\nu_T - 28.18\,(\Delta\nu_T/100)^2$$

where $\Delta\nu_T = \nu_{OH} - \nu_{CH_3}$ in Hz

The values obtained using this equation conformed closely to values obtained from a methanol calibration curve supplied with the instrument.

Full widths at half-heights were used for peak widths. The value for the lifetime, τ^*, at a given temperature was determined from the appropriate equation or, for **1**, by matching peak widths with those from computer-derived spectra. The computer program used was that of D'Agostino[7] and Macomber[8] for the interconversion of two A_n spin

systems. Equations used in the manual calculations were as follows: [3c]

$$\text{above } T_c \text{ (where } 1/\tau^* \gg 2\pi\Delta\nu\text{)}: \quad 1/\tau^* = \pi(\Delta\nu)^2(W^* - W')^{-1} \quad (1)$$

$$\text{at } T_c: \quad 1/\tau^* = \sqrt{2}\pi\Delta\nu \quad (2)$$

$$\text{below } T_c \text{ (where } 1/\tau^* \ll 2\pi\nu\text{)}: \quad 1/\tau^* = 2\pi(W^* - W') \quad (3)$$

where W^* and W' are the line widths in the presence and absence of exchange, respectively; the line width of the 4-methoxy group peak was used for W'. At each temperature the rate constant, k, was determined and a least-squares plot of ln k vs. $1/T$ yielded the Arrhenius activation energy, E_a. Values for $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta G^{\ddagger}$ were obtained from the appropriate equations.[3b] Alternately, $\Delta G^{\ddagger}$ was obtained from the Gutowsky–Holm approximation[6] (eq 2 above) and Eyring[3b] equation at the coalescence temperature. Errors were determined by a propagation of errors treatment.

Registry No.—**1**, 37706-47-1; **2**, 61770-02-3; **3**, 37706-46-0; **4**, 37706-35-7; (*N*-(2-benz[*h*]quinolylmethyl)-3,5-dimethoxybenzamide, 61770-03-4.

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Unusual Effect of Epoxidic Oxygen on the Ease of Base-Catalyzed Decomposition of Epidioxides

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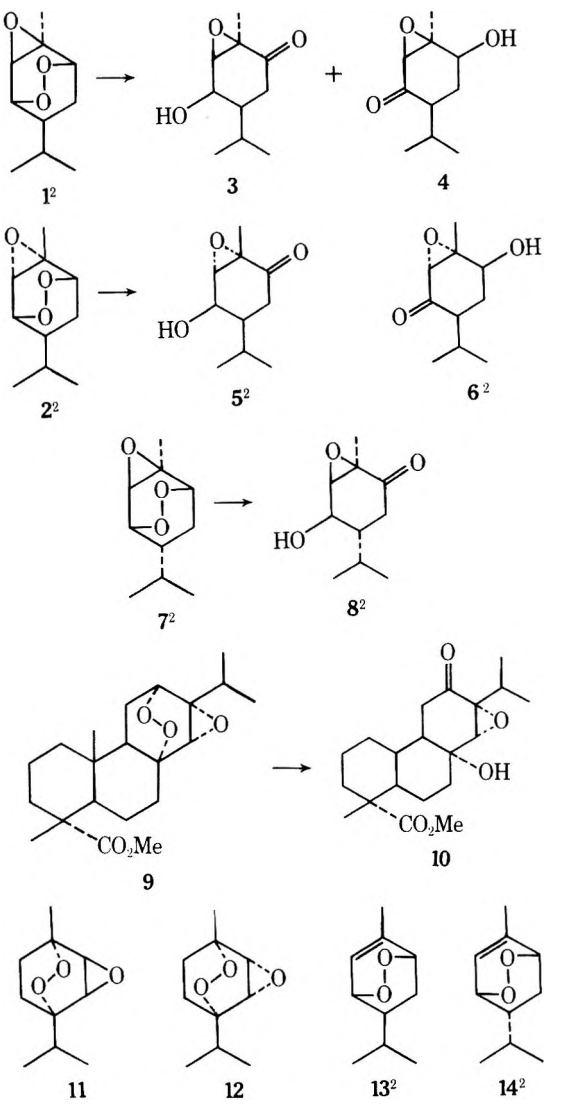
In a parallel study[2] we observed that attempts to separate a mixture of **1** and **2** by column chromatography or preparative TLC over silica gel resulted in rapid destruction of only one of the components, namely **1**. This peculiar selectivity attracted our attention and the reaction was examined in more detail.

Pure **1**, isolated by *rapid* preparative TLC followed by recrystallization, was stirred overnight with silica gel. TLC analysis indicated complete conversion to two new substances which were isolated by preparative TLC in 58 and 30% yield. Both compounds were isomeric hydroxy ketones (IR spectrum) which were differentiated by NMR spectrometry. The NMR spectrum of the major product **3** exhibited a somewhat broadened triplet at 4.28 ppm (J = 4.5 Hz, H-3) which was clearly coupled to a doublet at 3.66 ppm (H-2), whereas the minor product **4** had a triplet at 4.06 ppm (J = 7.5 Hz, 6) and a singlet at 3.12 ppm (H-2). Under these conditions **2** underwent no significant change, but prolonged stirring with silica gel (5 days) resulted in 51% recovery of **2** and 44% conversion

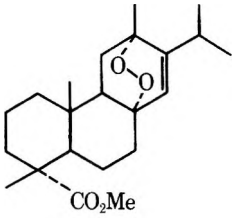


to the known[2] γ-hydroxy-α-epoxy ketone **5**. There was no evidence for formation of the isomeric hydroxy ketone **6**.[2]

The two cis epoxy epidioxides **7**[2] and **9**[5] also underwent essentially quantitative conversion to the γ-hydroxy-α-epoxy ketones **8** and **10** on stirring overnight with silica gel. On the other hand, neither **11** nor **12**, prepared by epoxidation of ascaridole in 48 and 32% yield, respectively, was affected by this procedure. The stereochemistry assigned to **11** and **12** is tentative; the minor, more polar isomer exhibited the signals of H-2 and H-3 as an AB system centered at 3.25 ppm (J = 5 Hz), whereas H-2 and H-3 of the major, less polar isomer were a two-proton singlet at 3.31 ppm. The same relationship of chemical shifts and polarities is characteristic of the cis and trans epoxy peroxides **1**[2] and **2**[2] and the cis and trans epoxy peroxides **21** and **22** (vide infra); however, formation of **11** in somewhat larger amount by attack from what appears to be the more hindered side seems surprising.

The 3,6-dihydro-1,2-dioxins **13**–**18**[2,7-9] were also stable toward silica gel[10] as were the mixtures of α- and β-epoxides **19** and **20** prepared by epoxidation of **16** and **17**.[8] Consequently the facile decomposition of epidioxides under the influence of silica gel depends on two factors: (1) the presence of a proton α to the epidioxide groups, presumably so that decomposition can take place by a process resembling the usual base-catalyzed decomposition of peroxides;[4] (2) the presence of a rigid system in which an epoxidic oxygen is situated cis and in close proximity to the epidioxide function.[12]

The reasons for the unusually facile decomposition of the



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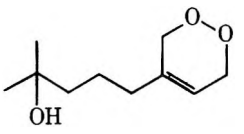

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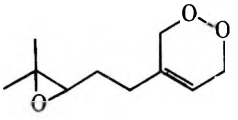
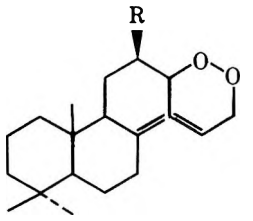
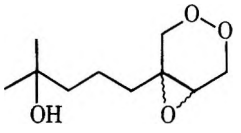


17[8]



18a, R = H[9]
b, R = OH[9]



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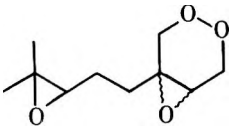

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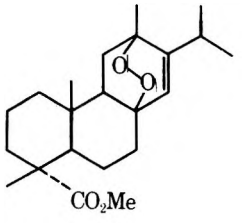
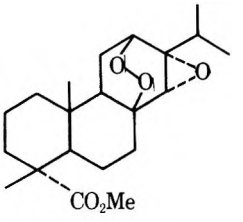


21[13]



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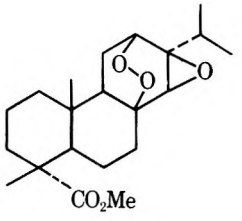

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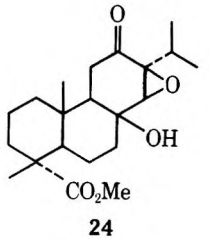
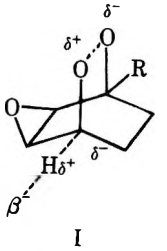


24

cis epoxy peroxides are obscure. One possibility is that transition state I in which one of the peroxidic oxygens must assume a partial positive charge is somehow stabilized by the epoxidic oxygen atom in the cis epoxide. Alternatively, the more polar cis epoxides might be more efficiently adsorbed on silica gel than the less polar trans epoxides and hence would be decomposed much more readily.



I

The generalizations presented in the preceding discussion provided a basis for assigning the correct stereochemistry to two substances obtained in approximately equal amounts by epoxidation of **21**.[13] The NMR spectrum of the crude reaction product revealed the presence of two isomers **22** and **23** (two H-14 singlets at 3.04 and 3.09 ppm).[14] Attempts to separate the mixture by preparative TLC resulted in isolation of a less polar epoxidic epidioxide (IR band at 1715 cm^{-1}, NMR singlet at 3.09 and multiplet at 4.37 ppm) and isolation of a more polar γ-hydroxy-α-keto epoxide (IR bands at 3500, 1720, and 1710 cm^{-1}; NMR singlet at 3.16 ppm). The hydroxy ketone must have been formed by rearrangement of **23**; hence its stereochemistry is represented by formula **24** and that of the unrearranged epoxy epidioxide is **22**.

Experimental Section[15]

Epoxidation of Ascaridole. A solution of 0.375 g of ascaridole and 500 mg of *m*-chloroperbenzoic acid in 20 mL of $CHCl_3$ was stirred for 10 days. The solution was washed thoroughly, dried, and evaporated and the two products were separated by preparative TLC (solvent 1:1 ether–hexane). The less polar epoxy peroxides,[11] wt 195 mg (48%), was repurified by preparative TLC and cyrstallized on drying: mp 42–44 °C; NMR signals at 3.31 (2 protons, H-2 and H-3), 1.31 (C-1 methyl), 1.01 d and 0.96 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.84.

The more polar product **12**, wt 133 mg (32%), was a gum which had NMR signals at 3.25 (center of AB system, J_{AB} = 5 Hz, H-2 and H-3), 1.30 (C-1 methyl), and 1.02 ppm d (J = 7 Hz, isopropyl methyls). The analytical sample was repurified by preparative TLC.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.91; H, 8.57.

Epoxidation of 16. A solution of 1.08 g of 16[8] and 1.3 g of *m*-chloroperbenzoic acid in 20 mL of $CHCl_3$ was stirred for 20 h and worked up as in the preceding section. This gave 1.02 g (93%) of gummy **19** (mixture of α- and β-epoxides) which was purified by preparative TLC (no indication of decomposition on the plate) and had an IR band at 3400 cm^{-1}; NMR signals at 4.33 d (J = 2 Hz, H-8), 4.24 (H-6a), 3.29+ (J = 2 Hz, H-7), and 1.20 ppm (two superimposed methyls).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.28; H, 9.12.

Reaction of this material with $FeSO_4 \cdot 7H_2O$ or $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2$[2] gave a complex mixture of products.

Epoxidation of 17. A solution of 0.800 g of 17[8] and 0.825 g of *m*-chloroperbenzoic acid in 25 mL of $CHCl_3$ was stirred overnight and worked up as usual. The gummy product, wt 0.804 g, presumably a mixture of epimers at C-3, C-6, and C-7, was further purified by TLC. There was no indication of decomposition on the plate. The material had NMR signals at 4.34 d (J = 2 Hz, H-8), 4.25 (H-9), 3.33 q (somewhat distorted, indicative of presence of a mixture, H-7), 2.70 tbr (J = 5 Hz, H-3), 1.28 and 1.25 ppm (two methyls).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.41; H, 8.19.

Epoxidation of 21. A solution of 0.120 g of 21[13] and 90 mg of *m*-chloroperbenzoic acid in 20 mL of $CHCl_3$ was refluxed for 3 h and then stirred overnight. The usual workup yielded a gum which was subjected to preparative TLC (two elutions with 2:5 ether–hexane) and gave 45 mg (36%) of less polar **22** and 45 mg (36%) of more polar **24**. In a second run using 0.200 mg of **21**, 86 mg (41%) of **22** and 80 mg (38%) of **24** were isolated. The less polar **22** (methyl 8β,12β-epidioxy-13α,14α-epoxyabieten-18-oate) proved difficult to recrystallize but finally formed crystals, mp 98–99 °C, which were suitable for elemental analysis and had IR bands at 1715 and 1242 cm^{-1}; NMR signals (90 MHz) at 4.37 m (H-12), 3.63 (methoxyl), 3.06 (H-14), 1.18 (C-4 methyl), 1.11 (C-10 methyl), 1.03 d and 0.96 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.24; H, 8.90; O, 21.60.

The more polar material **24** (methyl 13β,14β-epoxy-8β-hydroxy-12-oxoabietan-18-oate) was recrystallized from methanol–water: mp 161–162 °C; IR bands at 3500, 1720, 1710, and 1250 cm^{-1}; NMR signals (270 MHz) at 3.68 (methoxyl), 3.16 (H-14), 1.20 (C-4 methyl), 1.00 (C-10 methyl), 0.95 d and 0.86 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.00; H, 8.97; O, 21.90.

Reactions of Epoxy Peroxides with Silica Gel. Solutions of the peroxides in the appropriate solvent were stirred with 2 g of silica gel (Merck $PF_{254+366}$). The mixture was filtered and the silica gel was washed thoroughly with warm solvent. The combined filtrate and washings were evaporated to dryness at reduced pressure. The residue was analyzed by TLC, separated by preparative TLC when necessary, isolated, and identified.

A. 1[2] (0.200 g) in ether was stirred overnight and silica washed with warm $CHCl_3$. Preparative TLC of the residue (eluent 7:3 ether–hexane) gave 116 mg (58%) of **3** and 60 mg (30%) of **4**. There was no evi-

dence of starting material. Hydroxy ketone **3** crystallized on drying: mp 89–90 °C; IR bands at 3490 and 1695 cm^{-1}; NMR signals at 4.28 tbr (J = 5 Hz, H-3), 3.66 d (J = 4.5 Hz, H-2), 1.39 (C-1 methyl), 1.00 d and 0.90 ppm d (J = 7 Hz, isopropyl methyls).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.44; H, 8.85.

The gummy hydroxy ketone **4** had IR bands at 3440 and 1702 cm^{-1}; NMR signals at 4.06 t (J = 7.5 Hz, H-6), 3.12 (H-2), 1.52 (C-1 methyl), 0.93 d and 0.83 ppm d (J = 6.5 Hz, isopropyl methyls). For analysis, the sample was purified once more by preparative TLC.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.05; H, 8.80.

B. **2**[2] (0.200 g) under conditions A underwent no change. On stirring for 5 days, preparative TLC (1:1 hexane–ether) gave 51% of **2**, 44% of **5**.[2]

C. **7** (0.100 g) for 2 days, silica washed with warm $CHCl_3$, gave 94% of **8**.[2]

D. **9**[5] (0.100 g) overnight, silica washed with warm $CHCl_3$, gave a 100% yield of **10**.[5]

E. **19**[13] (0.100 g) for 2 weeks resulted in 99% recovery of starting material.

F. **20**[13] (0.100 g), 2 weeks, preparative TLC of product resulted in quantitative recovery of starting material.

G. **11** (0.100 g), 2 days, gave 96% of starting material.

H. **12** (0.040 g), 2 days, gave 95% of starting material.

I. **16**[13] (0.250 g), 2 weeks, gave quantitative recovery of starting material.

Registry No.—**1**, 61616-18-0; **2**, 61617-12-7; **3**, 61617-13-8; **4**, 61597-56-6; **5**, 61616-19-1; **7**, 61570-83-0; **8**, 61570-84-1; **9**, 25859-65-8; **10**, 34217-21-5; **11**, 61597-57-7; **12**, 61617-14-9; **16**, 57073-98-0; **17**, 56764-67-1; **19**, 61597-58-8; **20**, 61597-59-9; **21**, 5309-31-9; **22**, 61617-15-0; **24**, 61688-31-1; ascaridole, 512-85-6; $FeSO_4$, 19468-88-3.

References and Notes

(1) Supported in part by a grant from the Nationa Science Foundation (GP-12582).

(2) J. A. Turner and W. Herz, *J. Org. Chem.*, **42**, 1895 (1977) (see footnote 9 of this reference).

(3) Column chromatography of **1** or **2** over Florisil or basic alumina (Alcoa F-20) resulted in decomposition of both isomers to hydroxy ketones, presumably by the Kornblum–De La Mare mechanism.[4]

(4) N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951).

(5) W. Herz and R. C. Ligon, *J. Org. Chem.*, **37**, 1400 (1972).

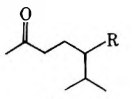
(6) G. O. Schenck, K. G. Kinkel, and W. J. Mertens, *Justus Liebigs Ann. Chem.*, **584**, 125 (1953); G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

(7) R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.*, **80**, 1438 (1958).

(8) M. Matsumoto and K. Kondo, *J. Org. Chem.*, **40**, 2259 (1975).

(9) J. A. Turner and W. Herz, *J. Org. Chem.*, **42**, 1900 (1977).

(10) Treatment of ia with basic alumina results in conversion to the hemiacetal ib which furnishes ic on chromatography over silica gel.[11] In our hands, column chromatography of **16–18** over silica gel yielded traces of the corresponding furans after several days' exposures, but preparative TLC over silica gel produced no change in the starting materials.



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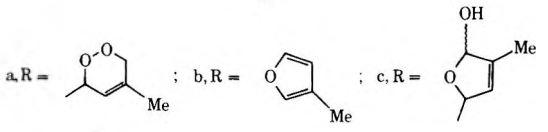

(11) E. Demole, C. Demole, and D. Berthot, *Helv. Chim. Acta*, **56**, 265 (1973).

(12) The most stable conformations of **19** and **20** are half-chair conformers **19a** and **19b** in which the O–O bond is not in the same relationship to the epoxide oxygen as in the cis epoxy dioxides **1**, **7**, **9**, and **22**.

19a **19b**

(13) W. Herz, R. C. Ligon, J. A. Turner, and J. F. Blount, *J. Org. Chem.*, **42**, 1885 (1977).

(14) By contrast, epoxidation of **15** where attack from the "β face" is severely restricted furnished only one isomer, i.e., **9**.[5]

(15) Experimental details are given in ref 2 and 13.

3-Carbo-*tert*-butoxybenzene Oxide

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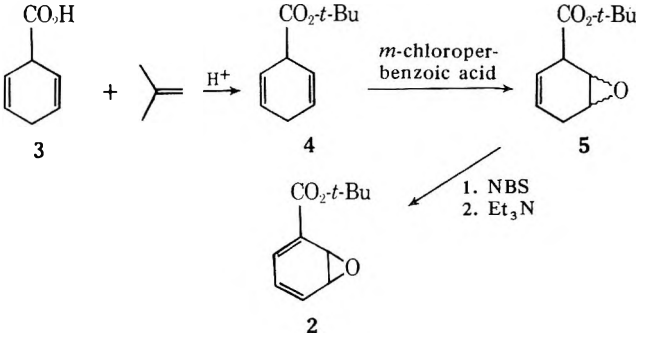
Since the initial synthesis of oxepin-benzene oxide was reported,[1] there has been considerable interest in the chemistry and biochemistry of arene oxides.[2–5] 4-Carbo-*tert*-butoxyoxepin-benzene oxide (**1**) has been prepared in these laboratories and, although **1** exists predominantly as the oxepin valence isomer,[6] nonetheless it reacts with nucleophiles at the 3 position of the benzene oxide valence isomer to afford *tert*-butyl trans-2-substituted 3-hydroxy-2,3-dihydrobenzoates.[6,7]

The synthesis of 3-carbo-*tert*-butoxybenzene oxide (**2**) was accomplished through a four-step procedure as indicated in Scheme I. Esterification of 1,4-dihydrobenzoic acid (**3**) with

Scheme I



isobutylene and acid catalysis afforded **4** (65%) that was oxidized with *m*-chloroperbenzoic acid to give a 1:1 mixture of *cis*- and *trans*-**5** (67%). The isomers could be separated by preparative GLC but were used as a mixture for subsequent reactions. Allylic bromination of **5** followed by treatment with Et_3N afforded **2** as a bright yellow oil (35%).

The spectral data indicate that **2** exists as the benzene oxide valence isomer, but the color of **2** suggests that the oxepin valence isomer is present to a small extent. Benzene oxide **2** is aromatized with aqueous acid to a 1:1.7 mixture of *m*- and *o*-hydroxybenzoic acids, respectively. Whereas **1** reacts readily with nucleophiles,[6,7] attempts to effect nucleophilic addition to **2** with HO^-, CH_3O^-, N_3^-, and $C_6H_5S^-$ gave either no reaction or a complex mixture of products.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. ^1H NMR spectra, unless otherwise indicated, were taken on a Varian Model T-60 spectrometer, and chemical shift data are reported in parts per million downfield from tetramethylsilane as an internal standard at 0.00. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6D mass spectrometer with an ionizing potential of 70 eV and are expressed in percent relative to the most intense peak. Except for the high mass region only the m/e's of greater than 20% relative intensity are listed. Melting points were taken on a Thomas-Hoover "Uni-Melt" and are corrected. Gas chromatographic analyses were carried out with a Hewlett-Packard Model 5750 gas chromatograph with thermal conductivity detectors. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***tert*-Butyl 1,4-Dihydrobenzoate (4).** Ester **4** was prepared in 65% yield from **3**[8] by the general procedure of McCloskey and Fonken:[9] bp 42–44 °C (0.2 Torr); IR (CCl_4) 3040, 1733, 1637, 1252, 1206 cm^{-1}; NMR (CCl_4) δ 1.45 (s, 9 H), 2.65 (d, 2 H, J = 9 Hz), 3.50 (t, 1 H, J = 9 Hz), 5.75 ppm (broad s, 4 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.86.

***cis*- and *trans-tert*-Butyl 2,3-Oxo-1,4-dihydrobenzoate (5).** To a stirring solution of 2.00 g (11.1 mmol) of **4** in 20 mL of CH_2Cl_2 at 0 °C was added a solution of 2.26 g (11.1 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2. After the addition was complete (0.5 h), the solution was stirred at 0 °C for an additional 0.5 h after which it was warmed to room temperature and stirred for 17 h. The solution was washed with three 25-mL portions of saturated aqueous Na_2CO_3 and 25 mL of saturated aqueous NaCl and dried (K_2CO_3). Filtration and evaporation under vacuum gave 2.08 g of a pale yellow oil. Distillation gave, after a small forerun, 1.40 g (67%) of *cis*- and *trans*-**5** as a colorless oil, bp 55–57 °C (0.2 Torr). GLC analysis (6 ft × 0.25 in, 15% SE-30, 130 °C) of the distillate showed the presence of the two isomers in a ratio of 1:1 with retention times of 11.8 (A) and 14.2 min (B). Preparative GLC provided pure samples of both isomers.

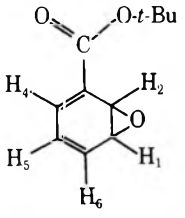
Isomer A: IR (CCl_4) 3055, 1730, 1370, 1288, 1258, 1150 cm^{-1}; NMR (CCl_4) δ 1.40 (s, 9 H), 2.4–2.6 (m, 2 H), 3.0–3.6 (m, 3 H), 5.4–5.6 ppm (m, 2 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.25.

Isomer B: IR (CCl_4) 3042, 1737, 1365, 1280, 1255, 1152 cm^{-1}; NMR (CCl_4) δ 1.50 (s, 9 H), 2.3–2.5 (m, 2 H), 3.0–3.6 (m, 3 H), 5.4–5.6 ppm (m, 2 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.13; H, 8.30.

3-Carbo-*tert*-butoxybenzene Oxide (2). To a solution of 11.32 g (57.7 mmol) of *cis*- and *trans*-**5** in 100 mL of CCl_4 was added 12.30 g (69.2 mmol) of finely ground *N*-bromosuccinimide. The suspension was stirred under reflux and irradiated with an ultraviolet lamp until the bromination was complete. The mixture was cooled to room temperature, filtered, and evaporated under vacuum to give 15.6 g (98%) of allylic bromide as a viscous yellow oil. The crude bromide was dissolved in 100 mL of diethyl ether and 7.30 g (72.1 mmol) of triethylamine was added in one portion. A crystalline salt precipitated immediately. The mixture was filtered to remove the salt; the filtrate was diluted with 100 mL of diethyl ether and washed with three 150-mL portions of water followed by repeated washings with 200-mL portions of 5% aqueous NaOH until the aqueous wash was colorless. The ether solution was dried (K_2CO_3), filtered, and evaporated under reduced pressure to give 11.1 g of a dark, viscous oil. Distillation through a short-path still afforded 3.87 g (35%) of **2** as a bright yellow oil: bp 60–65 °C (]/]5 Torr); IR (CCl_4) 1708, 1670, 1628, 1365, 1280, 1160 cm^{-1}; UV max (CH_3OH) 286 nm (ϵ 3100); UV max (isooctane) 283 nm (ϵ 4100); mass spectrum *m/e* 194 (8), 177 (8), 162 (15), 138 (24), 123 (17), 121 (17), 105 (23), 104 (32), 57 (33), 56 (26), 55 (23), 44 (45), 43 (44), 41 (100); NMR (220 MHz, CCl_4).[10]



	δ, ppm	*J*, Hz
H_1	4.29	$J_{1,2}$ = 2.75; $J_{1,5}$ = 1.65; $J_{1,6}$ = 4
H_2	4.91	$J_{2,4}$ = 2
H_4	6.90	$J_{4,5}$ = 7.05; $J_{4,6}$ = 1.3
H_5	6.26	$J_{5,6}$ = 8.45
H_6	6.34	
$(CH_3)_3C$	1.59	

Benzene oxide **2** formed a 1:1 adduct in 65% yield with maleic anhydride in benzene. It was recrystallized from benzene as white flakes: mp 176–177 °C; IR ($CHCl_3$) 1860, 1790, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 9 H), 3.3–3.9 (m, 5 H), 5.8–6.6 ppm (m, 2 H).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.90; H, 5.38.

Acid-Catalyzed Aromatization of 2. A solution of 100 mg of **2** in a mixture of 2 mL of CF_3CO_2H and 2 mL of water was stirred at room temperature. The solution was evaporated to dryness under reduced pressure, and the white, crystalline residue was dissolved in 1 mL of acetone. To the acetone solution was added 100 μL of *N*-trimethylsilyltrifluoroacetamide, and the resulting solution was analyzed by GLC (6 ft × 2 mm, 10% SE-30). The ratio of silylated *m*- and *o*-hydroxybenzoic acids was found to be 1:1.7 by comparison with authentic samples.

Acknowledgment. Financial support from the National Institutes of Health, Grant 1RO1-GM19103, is gratefully acknowledged.

Registry No.—**2**, 61812-51-9; 2 maleic anhydride adduct, 61812-48-4; **4**, 61812-52-0; **5**, 61812-53-1; maleic anhydride, 108-31-6.

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A Convenient Method for the α-Carbethoxylation of Alkylnitriles

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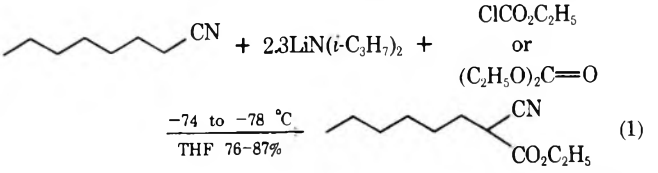
While carbethoxyl groups have been introduced in a number of instances into the α positions of acetonitriles substituted by phenyl groups,[2-4] only few examples are recorded when the acetonitriles are substituted by alkyl groups. With sodium ethoxide in diethyl carbonate[4] the yields are moderate and several hours heating at the boiling point and distillation of the ethanol produced are required to drive the reactions to products. Significant amounts of starting material are still recovered. For example, with this procedure capronitrile gives ethyl α-cyanocaproate in 54% yield along with starting material in 31% yield. An alternate procedure used by Hauser and Levine[5] to carbethoxylate acetonitrile with diethyl carbonate and sodium amide in refluxing ether gave ethyl cyanoacetate in only 40% yield and failed when extended to octanonitrile, octanamide forming instead in 30% yield after hydrolysis of the amidine intermediate.

Because alkylacetonitriles were recently monoalkylated[6] and benzeneselenylated[7] by way of the alkylacetonitrile anions formed using hindered dialkylamide bases, I attempted to carbethoxylate them analogously with diethyl carbonate or ethyl chloroformate. Using octanonitrile to optimize the conditions, it was found that 2.3 molar equiv of lithium diisopropylamide in tetrahydrofuran (THF) at −74 to −78 °C followed by 1.02–1.05 molar equiv of carbethoxylating agent gave high yields of ethyl hexylcyanoacetate (76–87%) after distillation (eq 1). Sodium hexamethyldisilamide gave lower



(1)

yields of product (see Table I). Diethyl carbonate was a better reagent to use than ethyl chloroformate, as the latter produced small amounts of ethyl *N,N*-diisopropylcarbamate as a side

Table I. Carbethoxylation of Octanonitrile

Base	Molar equiv base	Carbethoxylating agent	Rxn temp, °C	% yield	% GC purity
$NaN[Si(CH_3)_3]_2$	2.5	$(C_2H_5O)_2C{=}O$	RT	11	99
$NaN[Si(CH_3)_3]_2$	2.3	$ClCO_2C_2H_5$	RT	21	99
$NaN[Si(CH_3)_3]_2$	2.1	$ClCO_2C_2H_5$	−74	49	87
$LiN(i\text{-}Pr)_2$	2.3	$ClCO_2C_2H_5$	−74	85–87	98
$LiN(i\text{-}Pr)_2$	2.3	$(C_2H_5O)_2C{=}O$	−74	76	99

Table II. Carbethoxylation of Alkylacetonitriles

Registry no.	Nitrile	Molar equiv LDA	Molar equiv diethyl carbonate	Rxn temp, °C	% yield	% VPC purity	Bp, °C (mm)
625-28-5	Isovaleronitrile	2.4	1.02	−78	56	95	122–123 (41)[b]
628-73-9	Capronitrile	2.3	1.05	−78	76	97	119–120 (20)[c]
5732-87-6	Cyclopentylacetonitrile	2.0	1.05	−78	79	95	137–138 (19)[d]
4435-14-7	Cyclohexylacetonitrile	2.3	1.05	−78	86	97	147–148 (13)[e]
638-65-3	Stearonitrile	2.3	1.05	−15[a]	81		167–174 (0.15)[f]

[a] Stearonitrile is insoluble in THF at −78 °C. [b] Lit.[4] 111–113 °C (22 mm). [c] Lit.[4] 128–129 °C (23 mm). [d] Lit. 135–138 °C (17 mm),[9a] 129 °C (12 mm).[9b] [e] Lit. 146–148 °C (12 mm).[10] [f] Mp 36–37.5 °C, lit.[4] bp 167–180 °C (2 mm), lit.[4] mp 14–18 °C.

product, which could only be removed by careful fractional distillation.

The method was extended to other alkylacetonitriles and the yields of pure, distilled carbethoxylated product were excellent (Table II).

The α-carbethoxylation method was not devised to replace more classical approaches to these compounds such as cyanoacetate displacement of alkyl halides or Knoevenagel condensation–reduction sequences, but rather to provide a new alternative when such methods fail or cannot be applied in a synthesis of a more complex molecule.

Experimental Section

Ethyl Hexylcyanoacetate. To a flame-dried, N_2-flushed, three-necked 200-mL round-bottomed flask equipped with magnetic stirrer, N_2 inlet, stopper, and serum cap were added 4.75 g (47 mmol) of diisopropylamine and 40 mL of dry THF (freshly distilled from $LiAlH_4$). The solution was cooled to −74 °C (dry ice–2-propanol bath) and 29 mL of 1.6 N *n*-butyllithium in hexane (46 mmol, Foote Mineral Co., Exton, Pa.) was syringed in. The solution was stirred for 10 min at −74 °C and warmed to room temperature during 20 min. After cooling to −74 °C a solution of 2.50 g (20 mmol) of octanonitrile in 15 mL of THF was syringed in during 10 min, and the mixture was allowed to stir for 0.5 h at −74 °C and 0.5 h while it warmed to room temperature. The anion solution was then cooled to −74 °C and a 10-mL solution of 2.48 g (21 mmol) of diethyl carbonate in THF was syringed in during 10 min and allowed to stir for 2.5 h at −74 °C. The reaction was quenched with 10 mL of saturated NH_4Cl. Ether (75 mL) and water (20 mL) were added, and the layers separated. The organic layer was washed successively with 3 × 30 mL of 10% HCl, 3 × 30 mL of H_2O, and 30 mL of brine, and was dried over $MgSO_4$. Filtration and removal of solvent gave 3.86 g of a fragrant yellow oil, which upon fractional distillation (69–71 °C, 0.04 mm) gave 2.97 g of ethyl hexylcyanoacetate, analyzed to be 99% pure by GLC (10 ft × 0.125 in. column of 20% Apiezon L on 60/80 Chromosorb W, injector temperature 240 °C, column temperature 170 °C, detector temperature 280 °C). Lit. 149–150 °C (19 mm),[8a] 136–138 °C (14 mm).[8b] NMR (CCl_4) τ 5.69 (q, J = 7 Hz, 1.93 H), 6.54 (t, J = 7 Hz, 0.91 H), 8.05 (m, 2.50 H), 8.65 (m, 10.81 H), 9.10 (br t, 2.84 H). There are peaks in the IR spectrum (neat sample) at 2250 and 1750 cm^{-1}.

Acknowledgments. The author thanks Professor Thomas Katz for guidance and encouragement and the National Institutes of Health for support under Grant 5R01-GM-19173.

Registry No.—Ethyl isopropylcyanoacetate, 3213-49-8; ethyl butylcyanoacetate, 7391-39-1; ethyl cyclopentylcyanoacetate, 61788-30-5; ethyl cyclohexylcyanoacetate, 3213-50-1; ethyl hexadecylcyanoacetate, 61788-31-6; octanonitrile, 124-12-9; diethyl carbonate, 105-58-8; ethyl hexylcyanoacetate, 26526-76-1; ethyl chloroformate, 541-41-3.

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Application of Complex Formation to the Conformational Analysis of Thioxanthene Sulfoxides, Thianthrene Disulfoxides, and Phenoxathiin Sulfoxide Using Infrared Spectroscopy[1]

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The S–O stretching frequency of sulfoxides normally occurs at about 1050 cm^{-1}.[2] This rather intense vibration is not particularly influenced by the nature of the alkyl or aryl groups bonded to sulfur.[2] Consequently, this vibration has

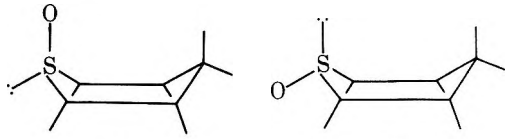
Table I. Infrared Spectra of Thioxanthene 10-Oxides and Related Systems

Registry no.	Compd	R_1	R_2	R_4	$R_{9a'}$	$R_{9e'}$	S(O)	ν_{S-O} (CCl_4), cm^{-1}	ν_{S-O} (CCl_4/ICl), cm^{-1}
61689-16-5	1	H	H	CH_3	H	H	a′	1035	950[a]
61689-17-6	2	Cl	H	CH_3	H	H	a′	1035	956[b]
19019-07-9	3	CH_3	H	Cl	H	H	a′	1040	959[c]
51517-43-2	4	CH_3	H	CH_3	H	H	a′	1035	947[d]
10133-81-0	5	H	H	H	H	H	e′	1041	989, 953
56195-77-8	6	H	H	H	C_2H_5	H	a′	1040	947
55235-94-4	7	H	H	H	$CH(CH_3)_2$	H	a′	1038	949
19018-81-6	8	H	H	H	CH_3	H	e′	1041	990[e]
56195-78-9	9	H	H	H	C_2H_5	H	e′	1042	989
19019-06-8	10	H	H	H	CH_3	CH_3	e′	1044	989
2748-51-8	11	H	H	H			e′,e′	1095	1005[f]
948-44-7	12	H	H	H			e′	1055	1005[g]

[a] 1008 cm^{-1} in $CHCl_3$; 970 cm^{-1} in CCl_4/I_2. [b] 1015 cm^{-1} in $CHCl_3$; 985 cm^{-1} in CCl_4/I_2. [c] 1020 cm^{-1} in $CHCl_3$; 985 cm^{-1} in CCl_4/I_2. [d] 1005 cm^{-1} in $CHCl_3$; 975 cm^{-1} in CCl_4/I_2. [e] 1036 cm^{-1} in $CHCl_3$; 1020 cm^{-1} in CCl_4/I_2. [f] This confirms the original assignment: T. Cairns, G. Eglinton, and D. T. Gibson, *Spectrochim. Acta*, **20**, 159 (1964): 1037 cm^{-1} in CCl_4/I_2. The trans isomer, containing both an a′ and e′ sulfinyl oxygen, produced absorptions at 955 and 991 cm^{-1}, respectively, in CCl_4/ICl. [g] This datum is for CCl_4/I_2. While decomposition in I_2 is sufficiently slow to obtain a spectrum, decomposition occurs too rapidly in ICl. 1035 cm^{-1} in $CHCl_3$.

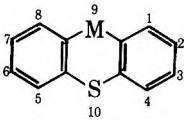
served as a useful analytical probe to determine the presence of the sulfinyl group but does not appear to have been used nearly as extensively as a conformational probe.[3] As part of our study of the stereochemistry of conformationally restricted diaryl sulfur systems[4] we now have examined the infrared spectra of a number of thioxanthene sulfoxides,[5] and similar systems, of known configuration and conformation and assigned them their S–O stretching frequency. Furthermore, we have examined the effect of complex formation upon the infrared spectra of thioxanthene derivatives of known geometry and demonstrated the value of complexation in determining the conformation of the sulfinyl group.

The sulfoxides examined in this study have either a pseudoaxial (a′) sulfinyl oxygen, I, or a pseudoequatorial (e′) sulfinyl oxygen, II. The geometry of these compounds, deduced



I II

by NMR, x-ray, and dipole moment studies, has been described in the literature.[4,5] The sulfinyl stretching vibration



thioxanthene, M = CH_2
thianthrene, M = S
phenoxanthiin, M = O

for all compounds was assigned using the method of Augdahl and Klaeboe.[6] In this procedure one compares the infrared spectrum in carbon tetrachloride and in carbon tetrachloride containing a halogen or mixed halogen (e.g., iodine or iodine monochloride). Addition of the complexing agent causes the weakening (or even disappearance) of the absorption due to the free sulfinyl group *and* the appearance of a new absorption assigned to the S–O···X_2 complex.[6,7] In several, randomly selected cases these assignments were supported by comparing infrared spectra in carbon tetrachloride and in chloroform, hydrogen bonding being known to shift ν_{S-O} to lower frequencies.[8] The sulfoxides examined include 4-methylthioxanthene 10-oxide (1), 1-chloro-4-methylthioxanthene 10-oxide (2), 4-chloro-1-methylthioxanthene 10-oxide (3), 1,4-dimethylthioxanthene 10-oxide (4), thioxanthene 10-oxide (5), *cis*-9-ethylthioxanthene 10-oxide (6), *cis*-9-isopropylthioxanthene 10-oxide (7), *trans*-9-methylthioxanthene 10-oxide (8), *trans*-9-ethylthioxanthene 10-oxide (9), 9,9-dimethylthioxanthene 10-oxide (10), *cis*-thianthrene 9,10-dioxide (11), and phenoxathiin 10-oxide (12).

The results of our study of the effect of the addition of iodine monochloride upon the S–O stretching frequency of thioxanthene sulfoxides are summarized in Table I. It can be seen that ν_{S-O} is quite insensitive to the conformation of the sulfinyl group. Thus, those compounds with an a′ sulfinyl oxygen absorb at approximately 1035 cm^{-1} while those which possess an e′ sulfinyl oxygen absorb at approximately 1042 cm^{-1}. While these are not exactly the same, a frequency difference of approximately 7 cm^{-1} would not, in our opinion, be a difference upon which to base a conformational analysis. Although $\Delta\nu_{S-O}$ is not very sensitive to conformation in these conformationally restricted diaryl sulfoxides, the new absorption of the complexed (with iodine monochloride) sulfinyl group is geometry dependent. Thus, the e′ S–O/ICl complexes exhibit an absorption at about 990 cm^{-1} while the a′ S–O/ICl complexes absorb at about 950 cm^{-1}. Like the uncomplexed absorptions, these bands are not very variable within a given family.

While iodine produced shifts of ν_{S-O} when several thioxanthene sulfoxides were examined, iodine monochloride is the reagent of choice in examining thioxanthene sulfoxides since it gives larger shifts and does not lead to rapid decomposition. Similarly, 11, which is known to exist in the diequatorial array, shows a smaller shift of ν_{S-O} in iodine than in iodine monochloride. This suggests that iodine monochloride is the reagent of choice in studying thianthrene oxides. While 12 decomposed rapidly in iodine monochloride/carbon tetrachloride, iodine was a sufficiently mild reagent to permit observation of $\Delta\nu_{S-O}$. Thus the phenoxathiin ring system is better studied using iodine than iodine monochloride. In general, the choice of complexing agent is dictated by the ease of decomposition of the complex, presumably through an intermediate cation.[9]

Most of the thioxanthene derivatives described in Table I are unlikely to alter conformation upon complexation either because of the substituents peri to the sulfinyl group[10] or because of the substitution at C-9.[4] However, that complexation may disturb a conformational distribution when such controlling factors are absent is suggested by the behavior of

thioxanthene oxides which lack substituents at C-4 and C-9. For example, three intense absorptions are found in the sulfinyl region[2] of the infrared spectrum of 2-chlorothioxanthene 10-oxide (carbon tetrachloride): 1101, 1081, and 1044 cm^{-1}.[11] In going to chloroform[11] only the absorption at 1044 cm^{-1} disappears while a new, broader absorption appears at 1035 cm^{-1}.[12] This unequivocally[8] assigns the 1044-cm^{-1} absorption (carbon tetrachloride) to ν_{S-O}. The corresponding absorption in **5** occurs at 1041 cm^{-1}. Addition of iodine monochloride to **5** (carbon tetrachloride) causes the absorption at 1041 cm^{-1} to diminish in intensity and produces two new absorptions—at 992 and 953 cm^{-1}. This suggests that the complex formed between **5** and iodine monochloride exists as a mixture of conformers.[13]

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer using solutions 0.02 M in solute and, where indicated, in complexing agent.

All of the compounds have been described by us or are available commercially.[4] No special purification procedures were employed in using iodine monochloride (commercially available).

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(13) We have demonstrated that thioxanthene sulfoxide assumes a predominantly a′ conformation in trifluoroacetic acid, presumably owing to increased size of the sulfinyl group upon hydrogen bonding to the solvent: A. L. Ternay, Jr., J. Herrmann, and B. R. Hayes, submitted for publication.

Synthesis of Dibenzyl Ethers via the Dehydration of Benzylic Alcohols in Dimethyl Sulfoxide

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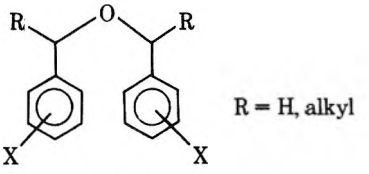
During the course of our investigations of intramolecular excimer formation of dibenzyl ethers,[1] we developed a general method of preparing substituted benzyl ethers of structure I in high yields from the respective alcohols using dimethyl



I

sulfoxide as the dehydrating agent. The ethers could be prepared with either electron-donating or electron-withdrawing substituents X, and with R = H or alkyl. This method was preferable to the Williamson synthesis or simple acid catalyzed dehydration which often gave low yields or mixtures of products.[2]

Dimethyl sulfoxide mediated dehydration of 1-alkylcycloalkanols and secondary and tertiary benzylic alcohols to olefins has been well documented by Traynelis and co-workers.[3,4] Me_2SO-catalyzed dehydration of diols to cyclic ethers has also been reported.[4,5] In both cases low ratios of alcohol to Me_2SO (1:3 to 1:12) were employed. When the ratio of alcohol to Me_2SO was raised to 1:1 or 3:1, more ether was produced at the expense of olefin, but the product still consisted of a complex mixture of olefin, ether, ketone, and starting material.[4]

We have observed that modification of earlier conditions[4] to very high ratios of alcohol:Me_2SO (16:1) completely suppresses the formation of olefins and oxidized products and provides high yields of ethers (Table I).

When lower ratios of alcohol to Me_2SO (12:1, 3:1) were tried, significant amounts of olefin and oxidized products were obtained. In general, secondary benzyl alcohols reacted faster than primary benzyl alcohols, and alcohols containing electron-donating groups on the ring reacted faster than those containing electron-withdrawing groups. Dehydration of *p*-methoxybenzyl alcohol proceeded smoothly in Me_2SO to give an 85% yield of ether, though it polymerized, rather than dehydrated, in the presence of sulfuric acid or $ZnCl_2$. An unsymmetrical cyclohexyl (α-methylbenzyl) ether also could be prepared if an excess of cyclohexanol were present in the reaction mixture.

A limitation of this method is indicated by the last entry in the table. No product was obtained upon heating *p*-nitrobenzyl alcohol in Me_2SO even after 22 h. It has been proposed that the radical decomposition of Me_2SO to strong acids is responsible for its apparent catalytic action in a variety of reactions.[6,7] The lack of reactivity of *p*-nitrobenzyl alcohol is therefore probably due to the presence of the radical quenching nitro group. In fact, addition of nitrobenzene was sufficient to significantly inhibit the reaction of *p*-methylbenzyl alcohol with Me_2SO presumably by preventing the production of strong acids.

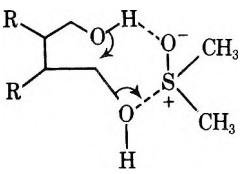
The reaction also appeared to be accelerated by oxygen. Thus, *p*-fluorobenzyl alcohol was unreactive in the presence of dimethyl sulfoxide at 175 °C under a nitrogen atmosphere, though it reacted completely after 8 h in air. This is consistent with other reports that oxygen is a requisite ingredient for the formation of strong acids from Me_2SO at elevated temperatures.[7,8]

The detailed mechanistic pathway of Me_2SO-catalyzed dehydrations has been the subject of some speculation. Traynelis has shown that a carbenium ion is implicated in the dehydration of alcohols to olefins in Me_2SO.[3,4] On the other hand, Gillis and Beck suggested an S_N2-type mechanism for the formation of tetrahydrofurans from 1,4-diols, where dimethyl sulfoxide aids in the removal of a proton from the attacking group while simultaneously stabilizing the leaving group (1).[5]

Table I. Dehydration of Benzyl Alcohols to Ethers in Dimethyl Sulfoxide[a]

Starting alcohol	Reaction time, h	Yield[b] of ether, %
α-Methylbenzyl alcohol	5[c]	99[d]
α-Methylbenzyl alcohol (+ fourfold excess of cyclohexanol)	3	65 (unsymmetrical ethers)
p-Methylbenzyl alcohol	3	89
p-Methoxybenzyl alcohol	0.5	85
p-Fluorobenzyl alcohol	8	99
p-Nitrobenzyl alcohol	22	

[a] Reactions were run using a 16:1 molar ratio of benzyl alcohol to Me_2SO. The reaction temperature was 175 °C. [b] Yields are for isolated, pure products. [c] Reaction was actually complete after 15–30 min. [d] Product consisted of a mixture of meso and *dl* ethers.



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If the intermolecular reaction of benzyl alcohols were proceeding through a cyclic transition state analogous to **1**, the dehydration of optically active α-methylbenzyl alcohol should give only meso product. However, when *l*-α-methylbenzyl alcohol (91% optically pure), resolved via its brucine salt,[9] was reacted with Me_2SO for 5 min at 175 °C, the NMR spectrum of the product indicated that it consisted of a nearly 50:50 mixture of the meso and *dl* ethers. Recovered starting material was found to be 77% racemized. These results together with the observed substituent effects on the reaction rate rule out a transition state such as **1**. Instead, an unimolecular pathway is indicated, although alkoxysulfonium salts may be involved. Further mechanistic studies are necessary to clarify the exact nature of the intermediate.

Experimental Section

Reagents and Materials. Dimethyl sulfoxide was obtained from the Fisher Scientific Co. and was dried over Linde type 3A molecular sieves before use. The starting alcohols were all available commercially and were used without further purification. Silica gel 60F-254 TLC plates were purchased from Merck and used to monitor all reactions. Silica gel 60 (70–230 mesh) obtained from Merck was heated overnight to 160 °C before use in the chromatographic separation of alcohols and ethers.

Sample Procedure for the Dehydration of Benzyl Alcohols. Two grams (0.0164 mol) of p-methylbenzyl alcohol and 0.08 g (0.001 mol) of dimethyl sulfoxide (molar ratio of 16:1) were heated to 175 °C for 3 h. The disappearance of starting material and appearance of product were monitored conveniently by thin layer chromatography (50% ether/hexane). The reaction mixture was chromatographed directly on a silica gel column giving 1.65 g (0.0073 mol, 89%) of bis(p-methylbenzyl) ether after removing solvent and drying in vacuo. The ethers obtained were pure by TLC and NMR.

Properties of the Substituted Dibenzyl Ethers. Bis(p-methylbenzyl) ether, mp 62–63 °C, reported[10] 63–63.5 °C; bis(p-methoxybenzyl) ether, mp 38–38.7 °C, reported[11] 39–39.5 °C; Bis(α-methylbenzyl) ether, bp (10 Torr) 144–150 °C, n^{23}_D 1.540, reported[2] bp (10 Torr) 145 °C, n^{20}_D 1.539.

Bis(p-fluorobenzyl) ether was previously unreported. Combustion analysis of our product gave satisfactory results (±0.2%) for carbon, hydrogen, and fluorine.

Cyclohexyl (α-methylbenzyl) ether was previously unreported. The NMR spectrum of our product was consistent with the ether structure.

Acknowledgments. We are grateful to the National Science Foundation (GM-05811) and to the Mobil Foundation for their financial support.

Registry No.—Me_2SO, 67-68-5; *l*-α-methylbenzyl alcohol, 1445-91-6; cyclohexanol, 108-93-0; p-methylbenzyl alcohol, 589-18-4; p-methoxybenzyl alcohol, 105-13-5; p-fluorobenzyl alcohol, 459-56-3; p-nitrobenzyl alcohol, 619-73-8; bis-(p-methylbenzyl) ether, 38460-98-9; bis-(p-methoxybenzyl) ether, 5405-95-8; *dl*-bis-(α-methylbenzyl) ether, 53776-69-5; *meso*-bis-(α-methylbenzyl) ether, 53776-68-4; bis-(p-fluorobenzyl) ether, 61812-54-2; cyclohexyl (α-methylbenzyl) ether, 61812-55-3.

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Fluoroisoprenyl Synthesis Using Ethyl 2-Fluoroacetoacetate[1]

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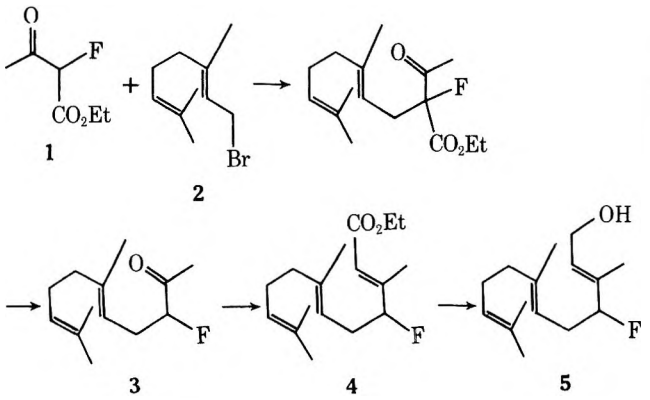
Fluorine substituted isoprenyl derivatives have aroused interest as potential insect juvenile hormone substitutes,[2] hyperlipidaemic drugs,[3] and, most recently, cancer chemotherapeutic agents.[4] The study of fluorinated isoprenoids in these and other contexts, however, has been hindered by a lack of convenient methods for their synthesis. Although 3-trifluoromethyl-2-butenol[5] and the 3-trifluoromethyl analogue of methyl farnesoate[2] have recently been prepared from trifluoroacetone and ethyl 1,1,1-trifluoroacetoacetate, respectively, most fluorinated isoprenyl compounds have been synthesized via schemes involving perchloryl fluoride fluorination.[3,6,12] The detonation hazards associated with this reagent,[7] however, discourage its use outside of specially equipped laboratories. We have developed a route to monofluorinated isoprenols involving base-catalyzed condensations of ethyl 2-fluoroacetoacetate (**1**), illustrated here by the preparation of 4-fluorofarnesol (**5**), whose general applicability is suggested by the widespread utility of ethyl acetoacetate itself in the assembly of carbon skeletons. Analogous condensations with ethyl 2-fluoroacetoacetate have not, to our knowledge, been previously reported.[8]

Ethyl 2-fluoroacetoacetate is readily prepared from inexpensive precursors, albeit in moderate yield, by base-promoted condensation of ethyl fluoroacetate and acetyl chloride.[8] Ethyl fluoroacetate is toxic but not otherwise hazardous,[9] and therefore can be handled with care by conventional techniques. Addition of geranyl bromide[10] to a solution of **1** in sodium methoxide–methanol gave in 63% isolated yield, after in situ base hydrolysis, 3-fluorogeranylacetone (**3**). Wadsworth–Emmons[11] condensation of **3** with diethyl 1-carboethoxyethylphosphonate gave ethyl 4-fluorofarnesoate (**4**)



as a 9:1 mixture of 2-*E* and 2-*Z* isomers. The assignment of stereochemistry to the two isomers was based on the relative position of the C-2 proton in their NMR spectra, that of the major (2-*E*) isomer appearing at 5.85 ppm, while that of the minor (2-*Z*) isomer appeared at 5.68 ppm. This downfield shift of the vinyl proton when cis to a fluorinated carbon has been demonstrated in closely related systems.[2,5] The assignment of 2-*E* stereochemistry to the major isomer is consistent with its longer GLC retention time.[13] Ethyl 4-fluorofarnesoate (**4**) was cleanly reduced by lithium aluminum hydride to the previously described 4-fluorofarnesol (**5**).[12]

Experimental Section

All reactions were carried out under strictly anhydrous conditions under a nitrogen atmosphere. Infrared spectra were run as thin films on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were taken on a Varian A-60A in $CDCl_3$. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane standard. Analytical GLC was performed on a Varian 2100 Model equipped with flame ionization detectors and 6 ft × 2 mm i.d. glass columns packed with 3% OV-225 on 100–200 mesh Varaport 30 (18 mL/min N_2 carrier gas). Mass spectra were obtained on an AEI MS-9 adapted to a chemical ionization mode (isobutane gas). Microanalyses were done by the Berkeley Microanalytical Laboratory.

6,10-Dimethyl-3-fluoro-5(*E*),9-undecadien-2-one (3).[6] Ethyl 2-fluoroacetoacetate[8] (1.092 g, 7.37 mmol) was added to 0.40 g (7.40 mmol) of sodium methoxide in 15 mL of anhydrous methanol at 0 °C. After 10 min, 1.54 g (7.1 mmol) of geranyl bromide[10] was added and the mixture stirred for 1 h at ambient temperature, at which time no starting bromide remained (TLC). A solution of 0.40 g of NaOH in 15 mL of H_2O was added and the mixture was refluxed for 3 h at 60 °C. After addition of 50 mL more of water, the mixture was exhaustively extracted with CH_2Cl_2, the extracts dried over $MgSO_4$, and the solvent removed. The crude orange oil thus obtained was bulb-to-bulb distilled (75 °C, 0.20 mm), yielding 0.9532 g (63%) of colorless oil (better than 96% pure by GLC): IR 1730 cm^{-1}; NMR 1.62 and 1.68 (singlets, 9 H, vinyl methyls), 2.00–2.17 (m, 4 H, allyl CH_2), 2.20 (d, J = 4.5 Hz, 3 H, $COCH_3$ coupled to fluorine), 2.53 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 4.67 (doublet of triplets, J = 50 and 6 Hz, 1 H, CHF), and 5.00–5.30 ppm (m, 2 H, vinyl H); CIMS *m/e* 213 (MH^+), 193 ($MH^+ - HF$). Anal. Calcd for $C_{13}H_{21}FO$: C, 73.54; H, 9.97. Found: C, 73.53; H, 9.93.

Ethyl 4-Fluorofarnesoate (4). Reaction of **3** with diethyl 1-carboethoxyethylphosphonate by the procedure of Machleidt[6] gave crude **4** as a 9:1 (by GLC) 2-*E* to 2-*Z* isomeric mixture (retention times at 150 °C: 20.25 and 12.75 min, respectively). Fractional distillation provided pure **4** in 69% isolated yield, the 2-*E*:2-*Z* isomer ratio increasing from about 1:1 in the first fraction to better than 99:1 in the final ones: 2-*E* isomer (bp 108–110 °C, 0.05 mm) IR 1725, 1660 cm^{-1}; NMR 1.27 (t, J = 7 Hz, 3 H, ethyl CH_3), 1.60 and 1.68 (singlets, 9 H, vinyl methyls), 1.97–2.20 (m, 4 H, allyl CH_2), 2.12 (d, J = 2 Hz, 3 H, 3-Me), 2.47 (doublet of triplets, J = 23 and 6 Hz, 2 H, CH_2CF), 4.15 (q, J = 7 Hz, 2 H, CH_2O), 4.82 (doublet of triplets, $J \simeq$ 50 and 6 Hz, 1 H, CHF), 4.90–5.33 (m, 2 H, vinyl H), and 5.85 ppm (m, 1 H, vinyl H); CIMS *m/e* 283 (MH^+), 263 ($MH^+ - HF$). Anal. Calcd for $C_{17}H_{27}FO_2$: C, 72.30; H, 9.64. Found: C, 72.07; H, 9.50. The 2-*Z* isomer had similar spectral properties, except for appearance of the C-2 vinyl proton in the NMR at 5.68 rather than 5.85 ppm.

4-Fluorofarnesol (5). Ester **4** was reduced with $LiAlH_4$ in 98% yield as previously described[12] to give **5**: IR 3325 cm^{-1} (OH); NMR 1.60 and 1.67 (singlets, 12 H, vinyl methyls), 1.98–2.17 (m, 4 H, allyl CH_2), 2.37 (doublet of triplets, J = 26 and 6 Hz, 2 H, CH_2CF), 2.93 (m, 1 H, OH), 4.02–4.33 (m, 2 H, CH_2O), 4.73 (doublet of triplets, $J \simeq$ 48 and 6 Hz, 1 H, CHF), 4.92–5.30 (m, 2 H, vinyl H), and 5.45–5.82 ppm (m, 1 H, vinyl H); CIMS *m/e* 241 (MH^+), 223 ($MH^+ - H_2O$), and 221 ($MH^+ - HF$). Anal. Calcd for $C_{15}H_{25}FO$: C, 74.95; H, 10.48. Found: C, 74.74; H, 10.43.

Registry No.—**1**, 1522-41-4; **2**, 6138-90-5; **3**, 61812-56-4; **4** (2*Z* isomer), 61812-57-5; **4** (2*E* isomer), 2599-71-5; **5**, 5979-63-5; diethyl 1-carboethoxyethylphosphonate, 3699-66-9.

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Aporphines. 23. Normorphothebaine Derivatives: Synthesis of an Aporphine Nitrogen Mustard

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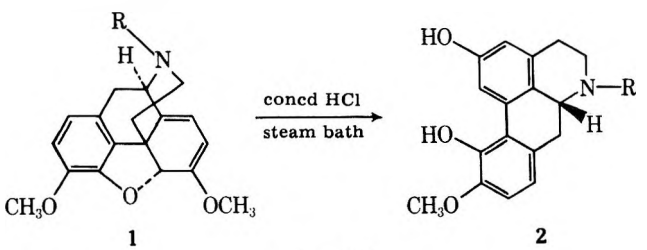
The known CNS activity[1-5] of a number of aporphine alkaloids led to the choice of this tetracyclic ring system for the synthesis of potential CNS penetrating antitumor agents bearing an alkylating function. The selection of normorphothebaine (**2b**) as the carrier base was governed chiefly by its ease of synthesis, its adaptability to large-scale preparations, and the availability of the natural alkaloid, thebaine. In the present communication we wish to report the synthesis of normorphothebaine (**2b**) and its derivatives, **3–5** and **7–10**.

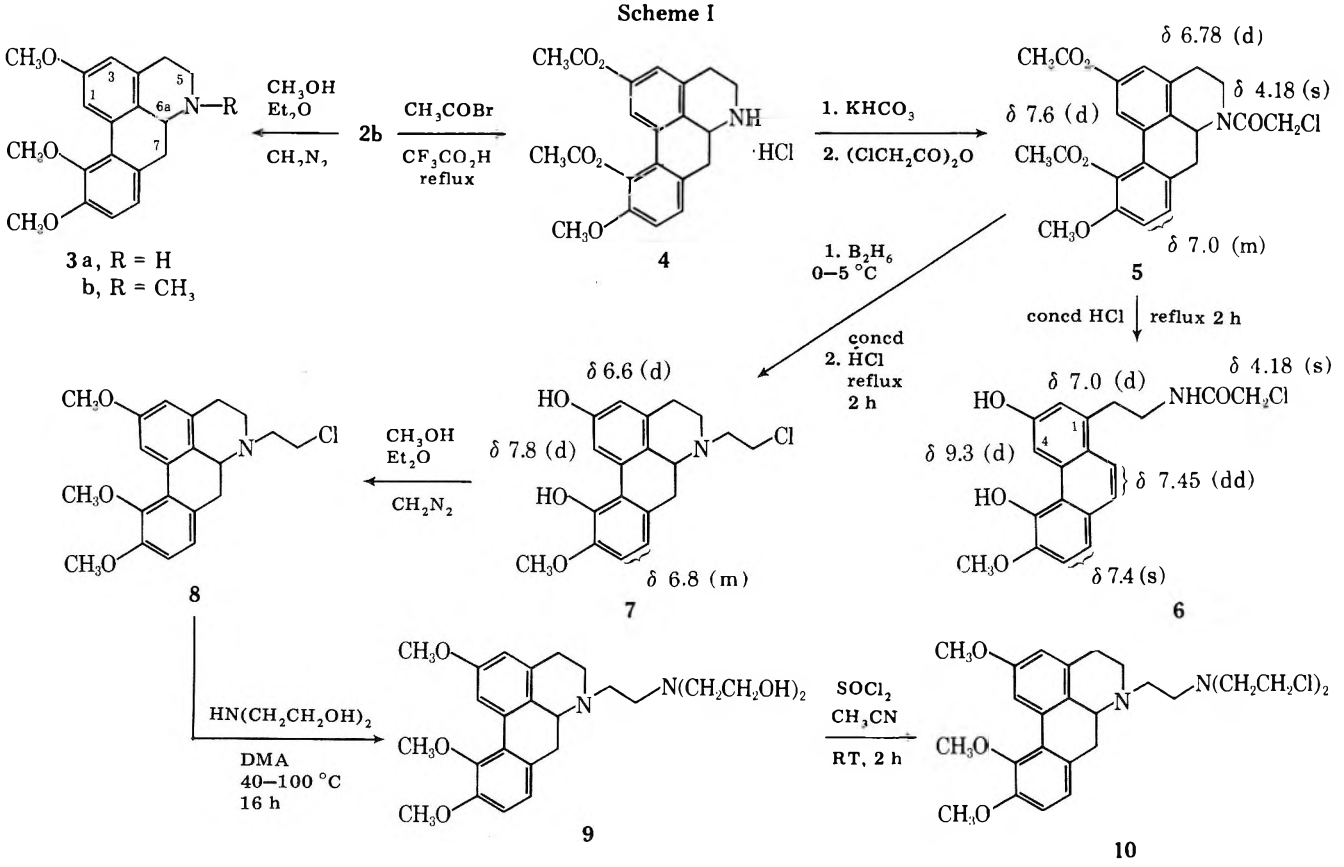
The rearrangement of morphine alkaloids to apomorphine derivatives has been hampered by the requirement of excessively strong acids (80–85% H_3PO_4 or CH_3SO_3H)[5,6] at high



1 **2**

a, R = CH_3
b, R = H

Scheme I



temperatures (145–150 °C), and occurs in only 10–25% yields. On the other hand, the rearrangement of thebaine (**1a**) proceeds in the presence of concentrated HCl at 95–100 °C in a sealed tube to morphothebaine (**2a**) in over 80% yield.[7a-d,8] Although several N-substituted northebaine derivatives have been described,[9] application of this method for the synthesis of derivatives of **2** has not been investigated.

Encouraged by the high yield of **2a** from **1a**, we embarked on the synthesis of the bis(chloroethyl) mustard derivative of normorphothebaine (**10**) shown in Scheme I. N-Demethylation of thebaine (**1a**) to northebaine (**1b**) using diethyl azodicarboxylate was achieved in 60% yield.[10] Rearrangement of northebaine (**1b**) to normorphothebaine (**2b**) was carried out in a sealed pressure bottle in concentrated HCl on a steam bath for 2.5 h. However, when the reaction was carried out in an open vessel, no precipitation of **2a** or **2b** occurred.[8] An attempt to methylate **2b** with diazomethane gave a mixture of **3a** and **3b** in a ratio of 3:1 in an overall yield of 65%. Acetylation of **2b** with CH_3COBr in refluxing CF_3CO_2H[11] gave **4** (45%) which further afforded the *N*-chloroacetyl derivative **5** (99%) by reaction with chloroacetic anhydride. Treatment of **5** with concentrated HCl led to scission of the nitrogen ring to give the phenanthrene analogue **6** (62%) whose structure was confirmed spectroscopically (NMR, UV, and MS). The NMR of **5** reveals that the proton at position 1 appears as a doublet at 7.6 ppm, whereas the proton at position 4 of **6** exhibits a doublet far downfield at 9.3 ppm, which is characteristic of phenanthrenes previously obtained by ring scission of other aporphines.[12-15] The mass spectrum of **5** shows the fragment *m/e* 366 as a result of cleavage of the chloroacetyl group from the molecular ion ($M^+ - COCH_2Cl$), as well as a fragment due to a retro-Diels–Alder, characteristic of the aporphine ring system.[16] On the other hand, **6** shows fragmentation due to the expulsion of $CH_2NHCOCH_2Cl$ (*m/e* 253) arising from cleavage of the carbon–carbon bond β to both the aromatic system and the heteroatom. Ring scission of aporphines to give phenanthrenes has been shown to occur in the presence of alkylating agents under basic conditions.[14,15] The formation of the phenanthrene **6** from **5** under acidic conditions is unique for an aporphine which, in this case, is apparently due to delocalization of the nitrogen electrons by the attached chloroacetyl group.

Reduction of **5** with B_2H_6 in tetrahydrofuran followed by hydrolysis with concentrated HCl afforded **7** (74%).

Treatment of **7** with diazomethane gave the trimethyl ether **8** (62%), which was further converted with diethanolamine in dimethylacetamide to give **9** (99%). The latter was readily converted to the chloro mustard **10** (53%) by reaction with $SOCl_2$.

Optical activity was retained for the entire sequence of reactions from **2b–10**.

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Samples for analysis were dried at 10^{-2} mm over silica gel at 55 °C. Thin layer chromatography (TLC) was performed on 7 × 3 cm precoated silica gel 13179, poly(ethylene terephthalate) foils (Eastman Kodak, Rochester, N.Y.) in solvent S_1 (EtOAc–MeOH, 2:1), S_2 (EtOAc–hexane, 1:1), S_3 (EtOAc–MeOH, 3:1), S_4 (EtOAc–MeOH, 2:1), S_5 (EtOAc–hexane, 6:4), S_6 (EtOAc–hexane, 6.5:3.5), and S_7 (EtOAc–MeOH, 9:1). Preparative TLC was carried out on silica gel plates (Analtech, 20 × 20 cm, 2000 μ). Column chromatography was performed on silica gel (Baker, 5-3405, 60–200 mesh). Detection was done in UV light (Mineralight) or with iodine vapors. The IR spectra were measured in $CHCl_3$ or KBr in a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were obtained using a Varian T-60 spectrometer in $CDCl_3$ or CD_3SOCD_3; $(CH_3)_4Si$ was used as an internal standard. The UV spectra were carried out in EtOH using a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141).

Tetrahydrofuran (THF), dimethylacetamide (DMA), and acetonitrile (CH_3CN) were distilled and dried over Linde Molecular Sieves. Thebaine was a product of S.B. Penick & Co., Lyndhurst, N.J.

Normorphothebaine (2,11-Dihydroxy-10-methoxynoraporphine Hydrochloride, 2b). A solution of northebaine[10] (5 g, 0.017

mol) in concentrated HCl (25 mL) was heated on the steam bath in a sealed pressure bottle for 2.5 h. The mixture was cooled and the dark precipitate was filtered and washed with 10 mL of cold concentrated HCl and 20 mL of cold EtOH. The crude product was heated on the steam bath with 50 mL of EtOH for 30 min, filtered, washed with 25 mL of cold EtOH, and dried to give 3.2 g of **2b** as a green, crystalline solid. Yields (60–70%) of **2b** were obtained. The product was washed with a small volume of cold MeOH, and the "wet" solid stirred with aqueous $KHCO_3$ for 2 h. The mixture was filtered, the solid dissolved in 20 mL of MeOH and filtered under N_2 pressure, and the dark filtrate acidified with ethereal HCl. A light tan hydrochloride separated which was homogeneous on TLC (S_1): mp 269–270 °C; NMR (CD_3SOCD_3) δ 7.8 (d, 1 H, C_1 H), 6.8 (m, 2 H, C_8 H and C_9 H), 6.5 (d, 1 H, C_3 H), 3.85 (s, 3 H, CH_3O), 3.2 (m, 7 H); UV max (EtOH) 300 nm (log ϵ 4.02), 278 (4.22), 270 (4.21), 220 (4.65); IR (KBr) 3250, 2920, 2800, 1600 cm^{-1}; $[\alpha]^{23}_D$ −119.8° (c 0.27, EtOH).

Anal. Calcd for $C_{17}H_{18}ClNO_3$: C, 63.86; H, 5.67; Cl, 11.09; N, 4.38. Found: C, 63.65; H, 5.72; Cl, 11.30; N, 4.29.

2,10,11-Trimethoxynoraporphine (3a) and 2,10,11-Trimethoxyaporphine (3b). A solution of **2b** (442 mg, 1.38 mmol) in MeOH (60 mL) was treated with diazomethane[17] (3 g, 0.076 mol) in Et_2O (300 mL). The solution was stirred for 16 h at room temperature and evaporated to dryness. The residue was dissolved in $CHCl_3$ and washed with 20% aqueous Na_2CO_3 and aqueous brine. The dried (Na_2SO_4) $CHCl_3$ solution was evaporated to dryness, and the resultant oil purified by preparative TLC (S_3). The slower moving band (R_f 0.18–0.41) was recovered to give **3a** (154 mg, 36%). The upper band (R_f 0.42–0.68) gave **3b** (130 mg, 29% yield).

NMR of **3a** ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.82–6.95 (m, 2 H, C_8 H and C_9 H), 6.65 (d, 1 H, C_3 H), 3.95 (s, 3 H, CH_3O), 3.90 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 2.6–3.3 (m, 7 H), 1.85 (s, 1 H, NH, D_2O exchanges); UV max (EtOH) 272 nm (log ϵ 4.09), 268 (4.10), 305 (3.73).

NMR of **3b** ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.95 (s, 1 H, C_9 H), 6.82 (s, 1 H, C_8 H), 6.65 (d, 1 H, C_3 H), 3.92 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 2.6–3.4 (m, 7 H), 2.55 (s, 3 H, NCH_3).

The desired product, **3a**, in MeOH–Et_2O (1:1) was acidified with ethereal HCl, yielding the hydrochloride salt of **3a** as a colorless solid, mp 260–263 °C.

Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; Cl, 10.19; N, 4.03. Found: C, 65.47; H, 6.37; Cl, 10.03; N, 3.96.

2,11-Diacetoxy-10-methoxynoraporphine Hydrochloride (4). A solution of 2b (8 g, 0.025 mol) in CF_3CO_2H (80 mL) was reacted with CH_3COBr (62.5 g, 0.51 mol) under cooling conditions, and then refluxed for 2.5 h under N_2. The solution was evaporated under reduced pressure, and ether was repetitively distilled from the residue to remove traces of CH_3COBr. The residue in $CHCl_3$ was shaken with aqueous $KHCO_3$, dried (Na_2SO_4), and evaporated. The residue was extracted with Et_2O, washed again with aqueous $KHCO_3$, dried (Na_2SO_4), and evaporated to give the free base of **4** as an oil (5 g, 45%). An analytical sample was obtained by preparative plate TLC (S_4) of 500 mg of the oil. The product was dissolved in Et_2O, washed with 2% aqueous NaOH and H_2O, dried (Na_2SO_4), and converted to the hydrochloride salt (4, 200 mg, mp 265 °C dec) using ethereal HCl, $[\alpha]^{23}_D$ −70.6° (c 0.59, 10% aqueous CH_3CO_2H).

Anal. Calcd for $C_{21}H_{22}ClNO_5$: C, 62.46; H, 5.49; Cl, 8.78; N, 3.47. Found: C, 62.33; H, 5.65; Cl, 8.90; H, 3.47.

Spectra of the free base of 4: NMR ($CDCl_3$) δ 7.6 (d, 1 H, C_1 H), 6.9–7.1 (m, 2 H, C_8 H and C_9 H), 6.9 (d, 1 H, C_3 H), 3.82 (s, 3 H, CH_3O), 2.6–3.2 (m, 7 H), 2.4 (2 s, 6 H, CH_3CO_2–), 2.2 (s, 1 H, NH, D_2O exchanges); UV max (EtOH) 265 nm (log ϵ 4.19), 310 (3.68); MS *m/e* 367 (M^+), 366 ($M^+ - 1$), 324 ($M^+ - CH_3CO$).

6-Chloroacetyl-2,11-diacetoxy-10-methoxynoraporphine (5). Chloroacetic anhydride (1.74 g, 0.010 mol) in CH_3CN (25 mL) was added dropwise to a solution of 4 (2.5 g, 0.0068 mol) in CH_3CN (60 mL) and Na_2CO_3 (1.4 g 0.013 mol). The mixture was stirred at room temperature for 16 h, filtered, and evaporated to dryness and the residue was dissolved in $CHCl_3$. The organic solution was shaken with 10% aqueous Na_2CO_3, dried (Na_2SO_4), and evaporated to give **5** as a near-colorless solid (3 g, 100%). A 2-g sample was chromatographed on a silica gel column (S_5, 250 mL, and S_6, 200 mL) giving 1.3 g of pure **5**: mp 110–115 °C; NMR ($CDCl_3$), see Scheme I; UV max (EtOH) 265 nm (log ϵ 4.09), 310 (3.38); MS *m/e* 443 (M^+), 401 ($M^+ - CH_3CO$), 366 ($M^+ - COCH_2Cl$); $[\alpha]^{23}_D$ −239.5° (c 0.58, EtOH).

Anal. Calcd for $C_{23}H_{22}ClNO_6$: C, 62.24; H, 5.12; Cl, 7.98; N. 3.15. Found: C, 62.11; H, 4.95; Cl, 8.12; N, 3.06.

1-(2-Chloroacetamido)ethyl-3,5-dihydroxy-6-methoxyphenanthrene (6). A suspension of **5** (200 mg, 0.45 mmol) in concentrated HCl (5 mL) was refluxed with stirring under N_2. During the heating complete solution occurred, followed by separation of an oil which slowly crystallized. After 2 h the mixture was cooled and filtered, and the product washed with 2 mL of cold concentrated HCl and cold CH_3CN and dried to give **6** (100 mg, 62%): mp 240–241 °C; NMR ($CDCl_3$), see Scheme I; UV max (EtOH) 225 nm (log ϵ 4.09), 242 (4.43), 258 (4.68), 290 (3.92), 310 (4.09), 319 (4.14); MS *m/e* 359 (M^+), 253 ($M^+ - CH_2NHCOCH_2Cl$).

Anal. Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; Cl, 9.85; N, 3.89. Found: C, 63.58; H, 5.15; Cl, 9.70; N, 3.87.

6-(2-Chloroethyl)-2,11-dihydroxy-10-methoxynoraporphine Hydrochloride (7). A solution of **5** (1.33 g, 0.003 mol) in THF (30 mL) was treated with 1 M diborane in THF (15 mL, 0.015 mol) at −5 to 0 °C and stirred at 5 °C for 17 h. Excess reagent was destroyed by dropwise addition of H_2O and the mixture evaporated to dryness. The residue was dissolved in $CHCl_3$, and the organic solution washed with H_2O and aqueous brine, dried (Na_2SO_4), and evaporated to give a colorless solid residue (1.32 g). An IR of the solid exhibited no carbonyl absorption at 1640 cm^{-1}, confirming reduction of the amide carbonyl. The product was suspended in concentrated HCl (25 mL) and the mixture refluxed with stirring under N_2 (considerable foaming) for 20 min. The suspension was cooled and filtered, and the solid washed with cold concentrated HCl, cold H_2O, CH_3CN, and Et_2O to give 0.85 g (74%). Recrystallization from a mixture of MeOH/Et_2O (1:2) gave **7** (0.45 g): mp 210–211 °C dec; NMR (CD_3SOCD_3), see Scheme I; UV max (EtOH) 270 nm (log ϵ 4.13), 278 (4.16), 305 (3.94); MS *m/e* 345 (M^+), 344 ($M^+ - H$), 296 ($M^+ - CH_2Cl$), 254 ($M^+ - CH_2NCH_2CH_2Cl$); $[\alpha]^{23}_D$ −66.6° (c 0.48, EtOH).

Anal. Calcd for $C_{19}H_{21}Cl_2NO_3$: C, 59.70; H, 5.54; Cl, 18.55; N, 3.66. Found: C, 59.84; H, 5.63; Cl, 18.30; N, 3.57.

6-(2-Chloroethyl)-2,10,11-trimethoxynoraporphine Hydrochloride (8). A solution of **7** (300 mg, 0.8 mmol) in MeOH (20 mL) was treated with CH_2N_2 (2 g, 23 mmol) in Et_2O (250 mL). After 1 h the mixture was filtered by N_2 pressure, and allowed to stand for 24 h at 5 °C. The solution was filtered, concentrated, diluted with more MeOH (15 mL), and treated once again with CH_2N_2 (1 g, 12 mmol) in Et_2O (125 mL). After standing for 5 days at 5 °C the solution was filtered, evaporated to dryness, and purified by preparative TLC (S_2) to give the free base of 8 as an oil: NMR ($CDCl_3$) δ 7.95 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H and C_9 H), 6.6 (d, 1 H, C_3 H), 3.90 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 3.60 (s, 3 H, CH_3O), 3.5–2.4 (m, 11 H); UV max (EtOH) 300 nm (log ϵ 3.82), 278 (4.17), 270 (4.19).

The oil was converted to the hydrochloride salt in the usual way, giving 8 (203 mg, 62%), mp 205–209 °C dec, $[\alpha]^{23}_D$ −112.7° (c 0.49, EtOH).

Anal. Calcd for $C_{21}H_{25}Cl_2NO_3$: C, 61.47; H, 6.14; Cl, 17.28; N, 3.41. Found: C, 61.45; H, 6.20; Cl, 17.12; N, 3.46.

6-[2-Bis(2-hydroxyethyl)aminoethyl]-2,10,11-trimethoxynoraporphine (9). A solution of 8 (0.53 g, 0.0014 mol) and diethanolamine (2 g, 0.019 mol) in dimethylacetamide (30 mL) was heated at 90–95 °C in the presence of KI (0.6 g, 0.0036 mol) for 16 h. The mixture was evaporated under reduced pressure at 50–60 °C, and the residue dissolved in $CHCl_3$. The organic solution was washed with 5 × 20 mL of H_2O, dried (Na_2SO_4), and evaporated to dryness to give **9** (615 mg, 99%): NMR ($CDCl_3$) δ 7.80 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H and C_9 H), 6.60 (d, 1 H, C_3 H), 4.1 (s, 2 H, OH), 3.9 (s, 3 H, CH_3O), 3.8 (s, 3 H, CH_3O), 3.7 (s, 3 H, CH_3O), 3.5 (m, 3 H), 3.3–2.6 (m, 16 H).

Without further purification, **9** was used directly for the preparation of **10**.

6-[2-Bis(2-chloroethyl)aminoethyl]-2,10,11-trimethoxynoraporphine Dihydrochloride Monohydrate (10). A solution of **9** (1.4 g, 0.0032 mol) in CH_3CN (50 mL) was treated at room temperature with $SOCl_2$ (4.1 g, 0.024 mol) dropwise with stirring under N_2. After stirring for 3 h at room temperature the solution was evaporated to dryness, and $CHCl_3$ distilled from the residue several times to remove traces of $SOCl_2$. The residue was dissolved in $CHCl_3$ and acidified with ethereal HCl, giving a dark, gummy precipitate which was triturated with Et_2O until crystallization occurred. The crude product was recrystallized from CH_3CN to give **10** (0.94 g, 53%), mp 235 °C dec, as a monohydrate: NMR ($CDCl_3$ + CD_3SOCD_3) δ 7.70 (d, 1 H, C_1 H), 6.8 (m, 2 H, C_8 H and C_9 H), 6.5 (d, 1 H, C_3 H), 3.1–4.0 (m, 19 H), 3.8 (s, 3 H, CH_3O), 3.7 (s, 3 H, CH_3O), 3.65 (s, 3 H, CH_3O); UV max (EtOH) 298 nm (log ϵ 4.03), 278 (4.28), 270 (4.30); IR (KBr) 3350 (br), 2350 (br), 1600 cm^{-1} (s); $[\alpha]^{23}_D$ −75.0° (c 0.26, EtOH).

Anal. Calcd for $C_{25}H_{36}Cl_4N_2O_4$: C, 52.64; H, 6.36; Cl, 24.86; N, 4.91; H_2O, 3.15. Found: C, 52.68; H, 6.36; Cl, 24.91, N, 4.91; H_2O, 3.38 (Karl Fischer).

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Registry No.—**1b**, 2579-67-1; **2b**, 61752-20-3; **3a**, 61752-21-4; **3a** HCl, 61752-22-5; **3b**, 61752-23-6; **4**, 61752-24-7; **4** free base, 61752-25-8; **5**, 61752-26-9; **6**, 61752-27-0; **7**, 61752-28-1; **8**, 61752-29-2; **8** free base, 61752-30-5; **9**, 61752-31-6; **10**, 61752-32-7; chloroacetic anhydride, 541-88-8; 6-(2-chloro-1-hydroxyethane)-2,11-diacetoxy-10-thoxynoraporphine, 62139-41-7.

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Electronic Structure of the Bicyclo[5.4.1]dodecapentaenylium Cation

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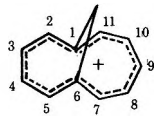
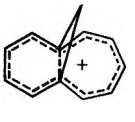
The structure of the bicyclo[5.4.1]dodecapentaenylium cation (1) has been the subject of some discussion in the recent literature. Vogel and co-workers[1b] have formulated the ion in terms of a perturbed [11]annulenium system (**1a**), whereas Masamune and co-workers[2] have suggested a benzohomotropenylium structure (**1b**). In a timely x-ray crystallographic



1a



1b

study, Destro, Pilati, and Simonetta[3] have concluded that **1** is quite similar to the neutral bridged [10]annulenes, on the basis of the 1–6 distance, which was found to be 2.299 Å.

In this communication we report a reinvestigation of the ion using the perturbational molecular orbital (PMO) theory,[4] as previously employed[5] in our general study of homoaromaticity.[6] In particular, we focus on the experimental bond lengths found for **1a** by Simonetta and co-workers.[3] In the treatment we adopt the peripheral (annulene) π-electron framework as reference system. In the presence of perturbations $\delta\beta_{kl}$ (to the resonance integrals of bonds k–l), the i–j bond order is changed by an amount δp_{ij}, where[5]

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}\, \delta\beta_{kl} \tag{1}$$

and $\pi_{ij,kl}$ is the mutual bond polarizability.

We consider specifically two perturbations to the electronic structure of the peripheral π-electron system which might be responsible for the variations in bond length observed in the bridged annulenes.[7] In the first case we allow for the dislocations in overlap which must occur in these systems, due to the pπ orbital misalignment. Following Heilbronner and co-workers[8] we introduce this factor as a perturbation to the resonance integrals (β_{kl}), which in this treatment take the value $\beta \cos\theta_{kl}$ (where θ_{kl} is the torsional angle about the bond k–l), thus $\delta\beta_{kl} = (\cos\theta_{kl} - 1)\beta$. In the second model account is taken of the possibility of a 1–6 homoaromatic interaction[5] ($\delta\beta_{kl} = \delta\beta_{16}$, where $\delta\beta_{16}$ is in units of β). Thus from eq 1 we obtain

$$\delta p_{ij} = \sum_{kl} \pi_{ij,kl}\, (\cos\theta_{kl} - 1) \tag{2}$$

(torsional model)

and

$$\delta p_{ij} = \pi_{ij,16}\delta\beta_{16} \tag{3}$$

(homoaromatic interaction model)

The results of these two perturbation schemes take slightly different forms, as the torsional angles (θ_{kl}) are directly available from crystallographic studies,[3,9] whereas the value of the homoaromatic interaction resonance integral ($\delta\beta_{16}$) is unknown (within the present context). Thus the δp_{ij} are obtained explicitly in the first case but only within a multiple of $\delta\beta_{16}$ in the second scheme. We adopt the well-known proportionality between bond lengths and bond orders[10] in the analysis (note, however, that we are considering perturbations to these quantities, rather than absolute values). Within the framework of this approximation, an increase in bond order is expected to lead to a decrease in bond length. We define

$$\delta r_{ij} = \bar{r} - r_{ij} \tag{4}$$

where $\bar{r}$ is the mean peripheral bond length. In such circumstance short bonds have positive δr_{ij}, and if the correlation between bond orders and bond lengths is valid there should be a direct proportionality between the δp_{ij} and δr_{ij}.

As a test of the scheme, we first analyze the x-ray crystallographic structure[9] of 1,6-methano[10]annulene (**2**)[11] in terms of the two perturbations discussed above. The results are presented in Table I, and it is immediately apparent that there is a strong correlation between the perturbed bond orders of the homoaromatic interaction model and the experimentally

Table I. Perturbed Bond Orders and Bond Lengths of 1,6-Methano[10]annulene (2)

Bond i–j	Torsional model[a,e] δp_{ij}	Homoaromatic interaction model[b,e] δp_{ij} (units of $\delta\beta_{16}$)	δr_{ij}[c,d]
1–2	−0.00601	−0.0631	−0.015
2–3	0.00384	0.0852	0.017
3–4	0.00433	−0.0442	−0.009

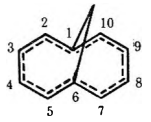
[a] Equation 2. [b] Equation 3. [c] Equation 4. $\bar{r}(2)$ = 1.400 Å. [d] Reference 9. [e] Correlation coefficient for zero intercept regression analysis: 0.327 (torsional), 0.993 (homoaromatic), 0.995 (bivariate analysis).

Table II. Perturbed Bond Orders and Bond Lengths of the 1,6-Methano[11]annulenium Cation (1)

Bond i–j	Torsional model[a,e] δp_{ij}	Homoaromatic interaction model[b,e] δp_{ij} (units of $\delta\beta_{16}$)	δr_{ij}[c,d]
3–4	0.00805	−0.0342	0.008
4–5	0.00020	0.0819	0.027
5–6	−0.01246	−0.0374	−0.030
6–7	0.01677	−0.0501	0.013
7–8	−0.01660	0.0286	−0.031
8–9	0.00807	−0.0059	0.018

[a] Equation 2. [b] Equation 3. [c] Equation 4. $\bar{r}(1)$ = 1.397 Å. [d] Reference 3. [e] Correlation coefficient for zero intercept regression analysis: 0.659 (torsional), 0.050 (homoaromatic), 0.959 (bivariate analysis).

observed variations in bond length. A bivariate regression analysis shows that the agreement is slightly improved if the torsional perturbations are also included. Nevertheless the results indicate that the small variations in the perimeter bond lengths of 2 originate primarily from the transannular 1–6 homoaromatic interaction.



2

In Table II we report the results of a similar analysis on the 1,6-methano[11]annulenium cation (1), and it is surprising to find that the homoaromatic interaction model, which was successful in the previous case, here completely fails (by itself) to reproduce the variations in bond lengths observed[3] for this molecule. On the other hand, reference to Table II shows that the torsional model performs quite well in this case; in particular the signs of the variations are all correctly reproduced. In fact, only the shortened bonds (positive δp_{ij} and δr_{ij}) are incorrectly ordered, and of these the most seriously in error appear to be 4–5 and 6–7, which are calculated to have increases in bond order which are too small and too large, respectively. Interestingly, the largest corrections to the bond orders from the homoaromatic interaction model occur for just these two bonds, and are of the correct sign to bring the perturbed bond orders into line with the experimental results. It would therefore seem that the slight misalignment of the pπ orbitals around the periphery of 1 is mainly responsible for the variations in bond length, together with a smaller, but important, contribution from the 1–6 homoaromatic interaction.

Why then is the 1–6 homoaromatic interaction more important for **2** than **1**? Of a number of possible explanations the most likely seems to be a reduction in the 1–6 overlap for **1** (note that the transannual interaction is calculated[5] to be slightly more favorable in **2**). Although the 1–6 distance is slightly longer in **1** (2.299 Å)[3] than in **2** (2.25 Å),[9] the variation in transannular overlap probably arises from the differing angles of the pπ orbitals at the 1 and 6 positions. We note that the dihedral angles of the bonds to the 1,6 atoms are 34.0° in **2**,[8,9] but only 24.9 and 16.3 in **1**.[3] Thus in the case of **2** the pπ orbitals at these positions should be bent further under the ring (anti to the bridge), and therefore will overlap more effectively (note that in **2** these orbitals lie in a symmetry plane and therefore point directly toward one another). In addition the "elastic ribbon principle", first enunciated by Heilbronner and co-workers,[8] may well be more effective in improving the peripheral overlap (at the expense of the transannular interactions) in a carbocation where the necessary polarization functions will be more accessible than in a neutral molecule.

Table III. Perturbed Charge Densities of the 1,6-Methano[11]annulenium Cation (1)

Position i	Torsional model[a] $\delta\xi_i$	Homoaromatic interaction model[b] $\delta\xi_i$ (units of $\delta\beta_{16}$)
4	−0.00471	−0.0572
5	0.00641	−0.0917
6	0.00025	−0.0131
7	−0.00183	0.1132
8	0.00838	−0.0062
9	−0.01347	0.1099

[a] Equation 6. [b] Equation 7.

Finally we consider the effects of the above perturbations ($\delta\beta_{kl}$) on the charge densities (ξ_i) of **1**. The perturbed charge densities $\delta\xi_i$ take the form[5]

$$\delta\xi_i = -\sum_{kl} \pi_{i,kl}\,\delta\beta_{kl} \tag{5}$$

where $\pi_{i,kl}$ is the atom-bond polarizability. Note that the $\delta\xi_i$ (unlike electron densities) are positive for increased cationic character (and vice versa). Thus

$$\delta\xi_i = -\sum_{kl} \pi_{i,kl}\,(\cos\theta_{kl} - 1) \tag{6}$$

(torsional model)

and

$$\delta\beta_i = -\pi_{i,16}\,\delta\beta_{16} \tag{7}$$

(homoaromatic interaction model)

The results of this analysis are presented in Table III. Vogel and co-workers[12] have drawn attention to the sensitivity of the ^{13}C NMR chemical shifts in the bridged annulenes to stereochemical factors (as against electronic effects). It is therefore not without misgivings that we compare our perturbed charge densities with the ^{13}C NMR chemical shifts observed for **1** by Masamune and co-workers.[2] Normally, of course (in the absence of nonplanarity and variations in hybridization), ^{13}C NMR chemical shifts can be used to obtain quite detailed information on π-electron charge distributions.[13] Nevertheless, it is clear that the perturbed charge densities derived from the homoaromatic interaction model bear a strong resemblance to the interpretation of the ^{13}C NMR chemical shifts of the ion given by Masamune and coworkers,[2] that is, transfer of electron density to positions 4(3), 5(2), and 8(10), with excess positive charge located at 7(11) and 9. The torsional perturbations appears to have little influence on the charge densities.

Acceptance of these data, of course, requires a dichotomy in the behavior of the bond orders and charge densities of **1**, the former depending mainly on the torsional angles, with the latter apparently being determined by the 1–6 homoaromatic interaction. There are at least three possible explanations for this divergence. (1) The ^{13}C NMR chemical shifts in **1** are not (primarily) determined by charge densities, and the agreement with the homoaromatic interaction model is purely fortuitous. (2) Nontransferability of parameters, that is, distinct properties require the consideration of different perturbations, to which they are especially sensitive. (3) The molecular structure of **1** is different in the solution[2] and solid[3] states. In this connection it is interesting to note that Vogel[1] has drawn attention to the similarity of the UV spectra observed for **1** and

the benzotropenylium cation (where the 1–6 interaction is, of course, well developed).

Perhaps more than anything, the results of this study highlight the complex interplay of perturbations which determine the electronic structure of the bridged annulenes. Similar conclusions have been drawn by other authors.[8,14]

Registry No.—**1**, 29534-58-5; **2**, 2443-46-1.

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Efficient Preparation of N^{α}-Formylamino Acid *tert*-Butyl Esters

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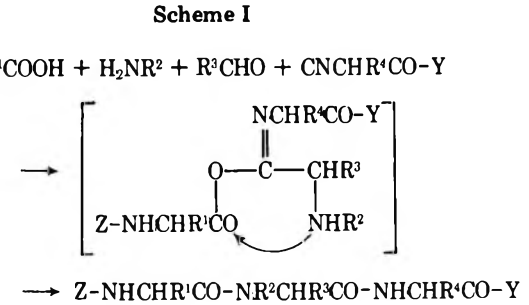
The formyl group has been a very useful amino-protecting group in peptide synthesis,[1] and could serve in combination with the selectively removable *tert*-butyl ester group in synthesizing suitably protected trifunctional amino acid derivatives. This study has been concerned with the development of an efficient procedure for preparing N^{α}-formylamino acid *tert*-butyl esters with minimal or no racemization. These compounds can be readily converted into isocyano acid *tert*-butyl esters required as one of the starting materials in four-component condensations (FCC). The FCC method of Ugi et al.[2] offers a unique and interesting new approach to peptide synthesis. In this reaction a carboxylic acid, an amine, and an aldehyde are combined with an isonitrile, such as an isocyano acid ester, to produce a tripeptide (Scheme I). Several known isocyano acid methyl (Y, OCH_3) and ethyl (Y, OC_2H_5) esters have been used in four-component condensations,[3] but *tert*-butyl isocyanoacetate[4-6] is the only known *tert*-butyl ester [Y, $C(CH_3)_3$] of an α-isocyano acid. These esters may be prepared by dehydration of intermediate N^{α}-formylamino acid esters.

Scheme I



Z = NH_2 protecting group
R^1, R^4 = amino acid side chain
R^2, R^3 = alkyl, aryl
Y = COOH protecting group

Known procedures for the preparation of N^{α}-formylamino acids proved to be unsatisfactory for producing their respective *tert*-butyl esters. The synthetic route to the preparation of N^{α}-formylglycine *tert*-butyl ester by treatment of *tert*-butyl chloroacetate with formamide[6] is not applicable to optically active amino acids without racemate resolution. Attempts at preparing *tert*-butyl esters of N^{α}-formylamino acids by the acid-catalyzed isobutylene procedure[7] provided the desired products, but only in very low yields. Standard N^{α}-formylation of amino acids or esters by formic acid and acetic anhydride[8] was incompatible with the *tert*-butyl ester group. However, the use of dicyclohexylcarbodiimide for the preparation of N^{α}-formylamino acid benzyl esters, reported by Thomas,[9] offered a route compatible with the *tert*-butyl protecting groups. We wish to describe a modified procedure for the efficient preparation of N^{α}-formylamino acid *tert*-butyl esters in high yields using formic anhydride[10] in pyridine.

Thus, dropwise addition of a preformed mixture consisting of formic acid (4 equiv) and dicyclohexylcarbodiimide (2 equiv) in chloroform at 0 °C to a solution of leucine *tert*-butyl ester in pyridine produced N^{α}-formylleucine *tert*-butyl ester (**2**) in 87% yield after purification by silica gel column chromatography, which removed a small amount of the side product 1,3-dicyclohexyl-1′,3′-diformylurea. The absence of racemized product was ascertained by converting **2** into N^{α}-formylleucine by treatment with trifluoroacetic acid and comparison of the product with an authentic sample[11] obtained by an independent procedure.[8] Other compounds prepared by our procedure are listed in Table IA.

The use of equivalent amounts or smaller excesses of reagents, i.e., 2 or 3 equiv of formic acid and 1 or 1.5 equiv of dicyclohexylcarbodiimide, resulted in considerably lower yields of **2** (28 or 57%, respectively). Attempts to prepare compound **2** by the isobutylene method[7] afforded the product in unacceptably low yields (17%).

The isocyano acid *tert*-butyl esters **5** and **6** were obtained from **1** and **2**, respectively, by dehydration with phosgene[3,13] followed by silica gel column chromatography in overall yields of 84 and 85% based on the starting amino acid *tert*-butyl esters.

Experimental Section

Amino acid *tert*-butyl esters were purchased from Bachem Inc., Marina Del Rey, Calif. Ester hydrochlorides were converted into free amines prior to use.[14] All optically active amino acids were of the L configuration.

***N*-Formylglycine *tert*-Butyl Ester (1).** A 2 M solution of formic acid in $CHCl_3$ (80 mL) was added dropwise with stirring and ice-bath cooling to a solution of dicyclohexylcarbodiimide (16.51 g, 80 mmol) in $CHCl_3$ (100 mL). The mixture was further stirred for 5 min, and then added with stirring over a period of 30 min into an ice-cold solution of glycine *tert*-butyl ester (5.25 g, 40 mmol) in pyridine (100

Table I

A. N^{α}-Formylamino Acid *tert*-Butyl Esters (For-AA-OBu^t)

Compd[a]	Formula[b]	Yield, %	R_f[c]	Bp, °C (mmHg)[d]	$[\alpha]^{25}_D$, deg, in EtOH
Gly (1)	$C_7H_{13}NO_3$	89	0.71	124–126 (0.5)	
Leu (2)	$C_{11}H_{21}NO_3$	87	0.79	143–144 (0.5)	−48.93 (c 2)
Pro (3)	$C_{10}H_{17}NO_3$	90	0.82	125.5–126.5 (0.6)	−109.79 (c 0.9)
Phe (4)	$C_{14}H_{19}NO_3$	88	0.83	171–172.5 (0.6)	15.97 (c 0.7)

B. 2-Isocyano Acid *tert*-Butyl Esters Derived from For-AA-OBu^t

Compd[a]	Parent amino acid	Formula[b]	Yield, %	R_f[c]	Bp, °C (mmHg)[d]	$[\alpha]^{25}_D$, deg, in EtOH
5	Gly	$C_7H_{11}NO_2$	94	0.90	91–93 (0.95)[e]	
6	Leu	$C_{11}H_{19}NO_2$	98	0.93	107 (0.45)[f]	−7.67 (c 1)

[a] NMR and IR spectral data agreed with the expected values. [b] Elemental analyses agreed with the calculated values within ±0.3%. [c] Solvent system for TLC (silica gel G) was $CHCl_3$–CH_3OH (96:4). [d] Boiling points were uncorrected. [e] Lit.[6] 87–89 °C (0.15 mm). [f] Compound 6 vaporized completely at this temperature.

mL). The mixture was then stirred for 4 h in an ice bath. Evaporation of the solvent was followed by addition of ether. The deposited dicyclohexylurea was removed by filtration and washed with ether. The combined filtrate was concentrated to an oil, which was purified by column chromatography on silica gel 60 (43 × 4.2 cm, 0.2–0.5 mm, E. Merck) using $CHCl_3$ followed by $CHCl_3$–CH_3OH (96:4) as eluents. Evaporation of the main peak fractions yielded 5.67 g of 1 as a colorless oil (89%). Several N^{α}-formylamino acid *tert*-butyl esters were prepared in this manner. The yields and physical constants of these compounds are summarized in Table IA.

A faster eluting side product was isolated by the above column chromatography and obtained as an oil (756 mg) which gradually crystallized. Recrystallization from ether–petroleum ether gave white needles. The compound was identified by NMR spectroscopy in $CDCl_3$ as 1,3-dicyclohexyl-1′,3′-diformylurea: mp 98.5–99.5 °C; R_f 0.94 (TLC, $CHCl_3$–CH_3OH, 96:4).

Anal. Calcd for $C_{15}H_{24}N_2O_3$ (280.4): C, 64.26; H, 8.63; N, 9.99. Found: C, 64.08; H, 8.68; N, 9.68.

***tert*-Butyl 2-Isocyanoacetate (5).** A solution of phosgene (990 mg, 10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a vigorously stirred solution of 1 (1.59 g, 10 mmol) and triethylamine (3.4 mL, 24 mmol) in CH_2Cl_2 (5 mL) at 0 °C over a period of 30 min. The solution was stirred for an additional 30 min, filtered, and the filtrate concentrated in vacuo. Ether was added to the residue followed by filtration and concentration. The residue was purified by chromatography on a silica gel column (20 × 2.4 cm) with $CHCl_3$ as an eluent. The fractions containing 5 were combined and evaporated to yield a pale yellow oil (1.33 g, 94% yield). For physical constants see Table IB.

***tert*-Butyl 2-Isocyano-4-methylvalerate (6).** Prepared in 98% yield from 2 (215 mg, 1 mmol) as described above, but using *N*-methylmorpholine as a base and a reaction temperature of −30 °C.[3] The filtrate was concentrated in vacuo. Benzene was added to the residue followed by filtration and concentration. Chromatographic purification afforded 6 as a pale yellow oil, see Table IB.

Registry No.—1, 51354-15-5; 2, 61900-40-1; 3, 61930-75-4; 4, 61900-41-2; 5, 2769-72-4; 6, 61900-42-3; formic acid, 64-18-6; glycine *tert*-butyl ester, 6456-74-2; leucine *tert*-butyl ester, 21691-53-2; proline *tert*-butyl ester, 2812-46-6; phenylalanine *tert*-butyl ester, 16874-17-2; 1,3-dicyclohexyl-1′,3′-diformylurea, 61900-29-6.

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Alkylation of 2-Naphthol by Alcohols in the Presence of Base[1]

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1-Alkyl-2-naphthols and their derivatives are useful as antibacterial substances and antioxidants.[2] These compounds have been obtained by acylation of 2-naphthol and subsequent reduction of the carbonyl group,[3] as a by-product of the Williamson ether synthesis from alkyl halide and sodium naphthyl oxide,[4] by heating a mixture of 2-naphthol or 2,2′-dihydroxy-1,1′-dinaphthylmethane, an excess of sodium methoxide, and methanol,[5] by dehydrogenation of 1-methyl-2-oxo-2,3,4,6,7,8-hexahydronaphthalene or of 1-propyl-2-hydroxy-5,8-dihydronaphthalene,[6] and by reaction of 2-naphthol with formaldehyde and thiols ($C_nH_{2n+1}SH$) in ethanol in the presence of triethylamine.[7]

The authors have found a novel method to synthesize 1-alkyl-2-naphthols in good yield by a one-step reaction from alkali 2-naphthyl oxide and alcohol in the absence of catalyst.

Results and Discussion

Heating potassium 2-naphthyl oxide in primary alcohol gave 1-alkyl-2-naphthol. The yields and physical properties (boiling point and melting point) of the 1-alkyl-2-naphthols so obtained are listed in Table I. When potassium 2-naphthyl oxide was heated in pentyl alcohol at 200 °C for 5 h, 1-pentyl-2-naphthol was not obtained. Good yields were obtained, however, in 5 h at temperatures higher than 260 °C. In the present reaction, benzyl alcohol and primary aliphatic alcohols with more than three carbon atoms were effective.

Table I. Yields and Physical Properties of 1-Alkyl-2-naphthols

$$2\text{-}C_{10}H_7OM + ROH \xrightarrow[2.\ H^+]{1.\ \text{heat}\ (-H_2O)} C_{10}H_6ROH[1\text{-}2]$$

M	Alkyl group (R)	Conditions: Temp, °C	Conditions: Time, h	Yield, %	Bp, °C (mmHg)	Mp, °C	Registry no.
K	$CH_3(CH_2)_2$	270	5	44	116–121 (1.5)		17324-09-3
K	$CH_3(CH_2)_3$	270	5	77	120–124 (0.15)	80.8[a]	50882-63-8
K	$(CH_3)_2CHCH_2$	280	5	54	154–156 (3)		52096-47-6
K	$CH_3(CH_2)_4$	280	5	79	142–144 (0.6)	81.6	13255-83-9
Na	$CH_3(CH_2)_4$	280	5	75			
K	$(CH_3)_2CH(CH_2)_2$	280	5	85	135–138 (0.1)		61769-84-4
K	$CH_3(CH_2)_5$	260	12	76	135–136 (0.25)		57744-65-7
K	$CH_3(CH_2)_5$	280	5	84			
K	$CH_3(CH_2)_6$	280	5	90	159–160 (0.7)		61769-85-5
K	$CH_3(CH_2)_7$	280	5	74	143–144 (0.1)		61351-11-9
K	$CH_3(CH_2)_{11}$	280	6	55	205–210 (2)		57744-66-8
K	$C_6H_5CH_2$	280	5	50	163–167 (0.2)	109[b]	36441-31-3

[a] Lit. 79–81 °C (ref 4). [b] Lit. 111–112 °C (ref 4).

A product with a boiling point of 154–156 °C (3 mmHg) obtained from the reaction of potassium 2-naphthyl oxide and isobutyl alcohol was analyzed by gas chromatography–mass spectrometry (GC–MS). The product contained two components and the mass spectra were similar; one is 1-isobutyl-2-naphthol and the other is probably a nuclear isomer. There is steric hindrance between the hydrogen atom at the 8 position and a bulky isobutyl group when substitution occurs at the 1 position of 2-naphthol. The isomer is presumably formed for this reason.

The structures of these products were determined by means of mass spectrum, NMR, and IR. As an example, the confirmation of 1-butyl-2-naphthol will be described here.

The molecular formula ($C_{14}H_{16}O$) was obtained by high-resolution mass spectrometry. The NMR spectra suggest strongly that a normal butyl chain is attached to the 1 position of the naphthalene nucleus; that is, the butyl group did not isomerize. The IR absorptions at 806 and 742 cm^{-1} also support the presence of 1,2 disubstitution. The structures of other products were confirmed by similar methods. In addition, the NMR spectra (in acetone, 60 MHz) due to the aromatic protons of 1-butyl-, 1-isobutyl-, 1-pentyl-, and 1-hexyl-2-naphthol were compared with each other. These spectra were identical in detail.

In addition to 1-alkyl-2-naphthol, polyalkyl-2-naphthols and 2-substituted alcohols were formed in the present reaction; the former are produced by further alkylation of 1-alkyl-2-naphthol and the latter by the Guerbet reaction (eq 1).[8]

$$2RCH_2CH_2OH \xrightarrow[-H_2O]{\text{base}} RCH_2CH_2CHRCH_2OH \qquad (1)$$

The formation of dialkyl-2-naphthols was confirmed by the GC–MS method, but the positions of the two substituents are not yet determined. These results are not listed in Table I.

Experimental Section

The NMR spectra were obtained on a JEOL JNM-C-60 HL (60 MHz) or PS-100 (100 MHz) spectrometer, with Me_4Si used as the internal standard. The mass spectra were obtained on a Hitachi mass spectrometer (RMU-6L) and on a Shimadzu mass spectrometer (LKB-9000), using an electron-accelerating voltage of 70 eV. The IR spectra were measured with a Japan Spectroscopic spectrometer (IRA-2). Gas chromatography was performed with a Yanagimoto apparatus (G-1800).

Alkylation. Because of the similarity of the procedures, only one example will be described in detail.

In a 300-mL autoclave, with an electromagnetic stirrer, were placed 9.61 g (0.0528 mol) of potassium 2-naphthyl oxide and 48.0 g (0.648 mol) of butyl alcohol. After the air had been replaced by nitrogen, the autoclave was heated at 270 °C for 5 h. The pressure reached 32 kg/cm^2. The autoclave was cooled, and the reaction mixture was washed with 3% aqueous sodium hydroxide, in which most 1-alkyl-2-naphthols are practically insoluble, then dilute hydrochloric acid, and dried over anhydrous magnesium sulfate. Vacuum distillation of the mixture, with 15-cm Widmer column, gave 1-butyl-2-naphthol in a 77% yield. The boiling point and melting point are given in Table I.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.79; H, 8.07. NMR (CCl_4, 100 MHz) δ 8.0–6.9 (m, 6 H), 4.82 (s, 1 H), 3.00 (t, 2 H), 1.8–1.2 (m, 4 H), 0.96 (triplet but with some distortion, 3 H).

A singlet peak appearing at δ 7.16 of 2-naphthol in acetone (60 MHz) (a proton at the 1 position) was completely absent from the spectrum of 1-butyl-2-naphthol.

Registry No.—Potassium 2-naphthyloxide, 36294-21-0; sodium 2-naphthyloxide, 875-83-2; propanol, 71-23-8; butyl alcohol, 71-36-3; isobutyl alcohol, 78-83-1; pentanol, 71-41-0; isopentyl alcohol, 123-51-3; hexanol, 111-27-3; heptanol, 111-70-6; octanol, 111-87-5; dodecanol, 112-53-8; benzyl alcohol, 100-51-6.

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The Importance of Alkene and Alkyne Structure on Their Relative Rates of Bromination

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The effect of solvent upon the relative rates of bromination of alkenes and alkynes has been explained in two different

Table I. Effect of Solvent and Structure of Alkene and Alkyne on Rates of Bromination

Solvent	Styrene, k_2, M^{-1} s^{-1}	Phenylacetylene, k_2, M^{-1} s^{-1}	k_o/k_a	*trans*-Cinnamic acid, k_2, M^{-1} s^{-1}	Phenylpropiolic acid, k_2, M^{-1} s^{-1}	k_o/k_a	4-Nitrocinnamic acid, k_2, M^{-1} s^{-1}	4-Nitrophenylpropiolic acid, k_2, M^{-1} s^{-1}
H_2O	1.1×10^7 [a]	3.1×10^4 [b,g]	360	$(1.27 \pm 0.01) \times 10^4$ [b]	$(6.70 \pm 0.06) \times 10^3$	1.90		
H_2O–CH_3OH 1:1	2.3×10^6 [a]	1.5×10^3 [g]	1590	73 ± 1	233 ± 2	0.31		
H_2O–CH_3OH 1:3				2.49 ± 0.01	17.3 ± 0.2	0.14		
CH_3OH	1.16×10^3 [a]	8.8×10^{-1} [c,g] 9.0×10^{-1} [d,g]	1318	$(2.40 \pm 0.03) \times 10^{-2}$	$(7.25 \pm 0.07) \times 10^{-3}$	3.32	1.7×10^{-2}	2.9×10^{-3}
CH_3OH				3.43 ± 0.05 [e]	3.16 ± 0.03 [e]	1.08 [e]		
0.075 N HCl in CH_3OH				0.108 ± 0.001	0.0436 ± 0.0004	2.47		
HOAc	11.2 [f]	4.33×10^{-3} [f]	2580					

[a] Reference 5. [b] 1% CH_3OH added to ensure solubility. [c] Direct measurement in absence of KBr. [d] Taken as the intercept of the plot $k_o(1 + K[Br^-])$ vs. $[Br^-]$. [e] Sodium salt. [f] Reference 4. [g] Unpublished data of G. Modena, F. Rivetti, and U. Tonellato, Centro Meccanismi di Reazioni Organiche del C.N.R. Istituto di Chimica Organica, Universita di Padova, 35100 Padova, Italy.

ways. One involves specific nucleophilic solvation of the positively charged carbon portion of the rate-determining transition state.[1-4] The other involves specific electrophilic solvation of the bromide ion in the rate-determining transition state.[5] In both of these explanations, the structure of the substrate has been largely ignored. We would like to present data which establish the importance of alkene and alkyne structure on their relative rates of bromination.

The rates of bromination, which are presented in Table I, were obtained by direct kinetic measurements. In the absence of KBr, the rate constants were obtained by following the disappearance of the bromine absorbance at 405–450 nm. For phenylacetylene, a second method was used. The rates were measured in the presence of KBr by following the disappearance of the Br_3^- complex at various wavelengths. The rate constant for the addition of free bromine was taken as the intercept of the plot of $k_0(1 + K[Br^-])$ vs. $[Br^-]$.[6] The rate constants obtained by these two methods are in good agreement. From the kinetic data, the ratios $k_{olefin}/k_{acetylene}$ (k_o/k_a) were calculated and are included in Table I.

The ratio k_o/k_a for the bromination of styrene and phenylacetylene in water given in Table I differs considerably from that reported previously.[4] Since the data in Table I were obtained by direct kinetic measurement, they are more reliable than those obtained previously by an indirect competition technique.

The data in Table I clearly indicate that a change in solvent has a large effect upon the rates of bromination of all four compounds studied. However, changing the solvent does not significantly alter the ratio k_o/k_a. This can best be illustrated by plotting $\log k_2^o$ vs. $\log k_2^a$ in the solvents studied. From the rates of bromination of styrene and phenylacetylene obtained in four solvents the following correlation is obtained.

$$\log k_2^a = 1.09 \log k_2^o - 3.45 \quad r = 0.996 \quad s \text{ (slope)} = 0.069$$

For the rates of bromination of cinnamic and phenylpropiolic acids in five solvents the following correlation is obtained:

$$\log k_2^a = 1.06 \log k_2^o - 0.013 \quad r = 0.972 \quad s \text{ (slope)} = 0.15$$

Clearly solvent changes have a similar effect upon the rates of bromination of alkenes and alkynes. However, the rate ratio k_o/k_a is strikingly different for the two series. For the pair styrene–phenylacetylene, the ratio is approximately 10^3 while for the acids the ratio is around 1.0.

Nucleophilic additions of Br_3^- to unsaturated carboxylic acids are known to occur. To rule out this mechanism, the rates of bromination of 4-nitrocinnamic and 4-nitrophenylpropiolic acids in methanol were determined. The rates are slower for bromination of the 4-nitro-substituted than the unsubstituted acids as shown in Table I. This result is consistent with an electrophilic addition of bromine and clearly establishes that the change in the k_o/k_a ratio is *not* due to a change in mechanism.

For the acids, there is a somewhat larger variation in the k_o/k_a ratio with changing solvent than for the styrene–phenylacetylene pair. This may be due to the fact that the rate constant for bromination of a carboxylic acid is actually a sum of two terms: one for the acid and one for the anion. The effect of changing solvent on the rate of bromination of these two species is similar but not identical. For example, the ratio k_o/k_a for bromination in 0.075 N HCl in methanol is 2.47. Under these conditions, the predominant species present are the undissociated acids. Bromination of the anions in methanol gives a ratio k_o/k_a of 1.08. While the two values are not substantially different, the difference is probably enough to cause the observed variation in the ratio k_o/k_a.

The data presented here clearly establish that the electrophilic bromination of alkenes is not always faster than for alkynes. Their relative rates depend greatly upon the structure of the substrate. While there is no doubt that electrophilic solvation of the departing bromide ion is important, solvation of the organic portion in the rate-determining transition state is also important. It is not yet clear if this effect is specific nucleophilic solvation or a general medium effect on the ground or transition states.

Experimental Section

Materials. *trans*-Cinnamic, phenylpropiolic, *p*-nitrocinnamic, and *p*-nitrophenylpropiolic acids were commercially available and were purified by crystallization.

Sodium cinnamate and phenylpropiolate were prepared by neutralizing the acid with a stoichiometric amount of 1 N solution of NaOH in aqueous methanol, and evaporating to dryness followed by crystallization from aqueous methanol.

Methyl alcohol was refluxed with Br_2 and then distilled twice from bromine and K_2CO_3.[7] Distilled water was prepared by the method of Harbison.[8] The solution of HCl in MeOH was prepared by passing dry HCl gas through methanol. The HCl concentration was determined by standard titration with 0.1 N aqueous NaOH.

Kinetics. The rates of addition to the olefins and acetylenes were measured using a Durrum-Gibson stopped flow spectrophotometric system or Cary 16 spectrophotometer as previously reported.[9,10] The consumption of bromine was measured by the decrease in the absorption at 490 mm. The reported rate coefficients are the mean values of two to seven independent determinations.

Second-order rate constants were determined under pseudo-first-order conditions, Br_2 concentration $\simeq 5 \times 10^{-4}$ M, excess of unsaturated substrate varied from 160 to 20 (for phenylpropiolic acid due to low solubility in water only tenfold excess of substrate was used).

The second-order rate constant of *trans*-cinnamic acid in water was determined at comparable concentrations of both substrates, both being about 5×10^{-4} m and containing 1% of CH_3OH to ensure solubility. For runs carried out on a Cary 16 spectrophotometer, a 10-cm cell was used to obtain the absorption change of ca. 0.2 absorbance unit.

Acknowledgment. Continued financial support by the National Research Council of Canada is gratefully acknowledged. We also thank Professor G. Modena, Istituto di Chimica Organica, Universita di Padova, Padova, Italy, for permission to use his data.

Registry No.—Styrene, 100-42-5; phenylacetylene, 536-74-3; *trans*-cinnamic acid, 140-10-3; sodium cinnamate, 18509-03-0; phenylpropiolic acid, 637-44-5; sodium phenylpropiolate, 7063-23-2; *p*-nitrocinnamic acid, 619-89-6; *p*-nitrophenylpropiolic acid, 2216-24-2.

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Unusual Shielding Effects in the Proton Nuclear Magnetic Resonance Spectrum of 1-Methyl-3-phospholene 1-Oxide

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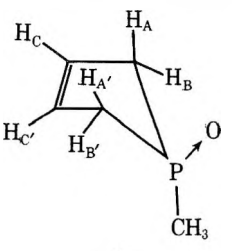
In the course of a study of the chemical and physical properties of phospholene derivatives[1-4] we were puzzled by the ^1H NMR spectrum of one of the compounds of this class, 1-methyl-3-phospholene 1-oxide[3] (I). In agreement with a



I

previous report[5] we found that a solution of I in $CDCl_3$ showed a simple 60-MHz ^1H NMR pattern consisting of three doublets (due to coupling with ^{31}P), for CH_3 at δ 1.60 ($^2J_{HCP}$ = 13 Hz), CH_2 at δ 2.43 ($^2J_{HCP}$ = 11 Hz), and CH at δ 5.87 ppm ($^3J_{HCCP}$ = 28 Hz), suggesting a high degree of symmetry for the molecule. From such spectra it was concluded earlier[5] that protons H_A and H_B in I fail to show the nonequivalence expected of protons in cis and in trans position to the P→O bond, relative to the plane of the ring. Although the ^1H NMR spectrum of the phospholene derived from I, obtained by reduction of the tertiary phosphine oxide I to the corresponding tertiary phosphine, did show nonequivalent protons[5] H_A and H_B and thus suggests an AA'BB'X pattern (X = ^{31}P), no explanation was advanced for the inconsistency in the ^1H NMR spectrum of I.

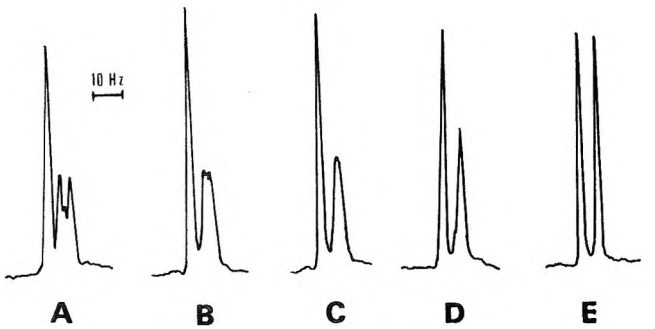


Figure 1. ^1H NMR spectrum (Varian T-60) of the CH_2 protons in 1-methyl-3-phospholene 1-oxide at various dilutions; A, neat; B, 0.2 parts; C, 0.3 parts; D, 0.5 parts; E, 1 part of $CDCl_3$ (v/v).

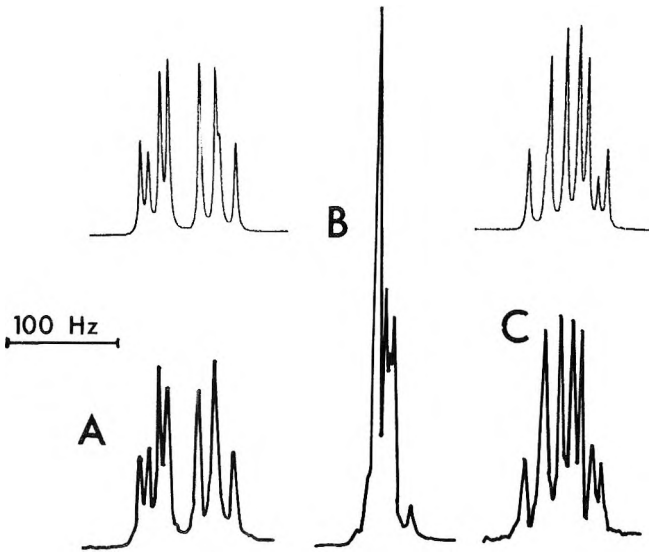


Figure 2. Experimental (bottom) and computer-simulated (top) 270-MHz ^1H NMR spectra of the CH_2 protons in 1-methyl-3-phospholene 1-oxide; A, neat (at 50 °C); B, 50% solution in $CDCl_3$ at room temperature; C, 9% solution in $CDCl_3$ at room temperature.

Nonequivalence of the methylene protons was also observed for the sulfide[1] derived from I and for the 1-chloro- and 1-hydroxy-3-phospholene 1-sulfides.[4] In view of these observations and of the known rigidity of the stereochemistry around the phosphorus atom, the ^1H NMR pattern obtained for I was difficult to rationalize. We, therefore, undertook a more detailed study of concentration and temperature effects on the ^1H NMR spectra of the methylene protons of I.

Results and Discussion

Proton spectra of I recorded at room temperature and at 60 MHz in the neat state and at various degrees of dilution in $CDCl_3$ are shown in Figure 1. Surprisingly, with increasing dilution, the initially complex methylene proton spectrum simplifies to the doublet reported earlier.[5] This effect is also shown upon dilution with benzene as solvent.

Two possible explanations suggest themselves for this observation: (a) a dynamical effect, which renders the A and B protons equivalent within the NMR time scale, or (b) an accidental simplification of an AA'BB'X spectrum. In order to shed more light on this problem proton spectra were obtained at 270 MHz as shown in Figure 2 for the following concen-

Table I. NMR Parameters[a] (in Hertz at 270 MHz) of the CH_2 Protons in 1-Methyl-3-phospholene 1-Oxide

	Neat	9% solution ($CDCl_3$)
$\delta_A - \delta_B$	−53.2	+35.5[b]
$\lvert^2J_{AB}\rvert$	17.4	17.64
$^2J_{AP}$	±14.32	±16.04[c]
$^2J_{BP}$	∓7.95	∓9.18[c]

[a] The olefinic protons H_C give rise to a clean doublet due to coupling with ^{31}P and show no evidence of coupling with the methylene protons H_A and H_B. [b] Absolute shifts: H_A, 2.59; H_B, 2.47 ppm. [c] H_A in I is cis to P→O in accordance with J and δ assignments made for 1,2,5-trimethyl-3-phospholene 1-oxide.[7]

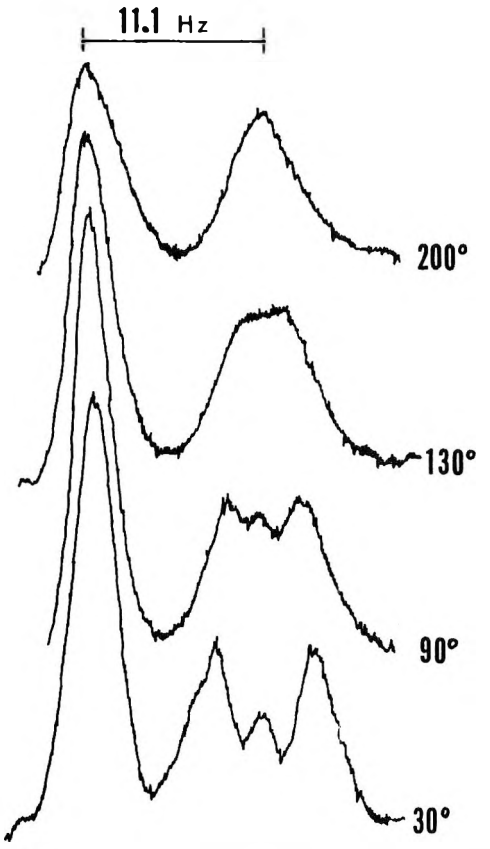


Figure 3. ^1H NMR spectrum (Varian A-50/60) of the CH_2 protons in a neat sample of 1-methyl-3-phospholene 1-oxide at various temperatures.

trations: neat sample I, 50 and 9% solutions of I in $CDCl_3$. The spectrum of the neat sample had to be recorded at 50 °C because of the difficulty of preventing the sample from crystallizing at room temperature. The others were recorded at room temperature. In view of the temperature effect discussed below, the spectrum of the neat sample is, therefore, not directly comparable with the corresponding 60-MHz spectrum. The spectra of the neat compound and of the 9% solution, however, are satisfactorily interpreted in terms of the AB part of ABX spectra,[6] with the parameters summarized in Table I. Computer-simulated spectra of I for the two cases of Table I are also shown in Figure 2. While the coupling constants are only slightly affected (to within 12%) by dilution, the chemical shifts reflect an inversion in the relative shielding experienced by A and B.

The spectrum of the 50% solution in Figure 2 cannot be understood as an AB part of an ABX pattern; however, computer simulations revealed that it could qualitatively be explained as the AA′BB′ part of an AA′BB′X pattern. Exact parameters were not obtained because of the insufficiency of actual experimental values provided by the spectrum in Figure 2.

These observations show clearly that the methylene protons A and B of I are nonequivalent, basically giving rise to an AA′BB′ spectrum, which degenerates, under proper conditions of the environment (dilution, temperature), into apparent ABX or even A_2X spectra.

The temperature dependence of a neat sample at 60 MHz is shown in Figure 3. With increasing temperature the spectrum becomes simpler and more symmetrical, in a way similar to the effect observed upon dilution at 60 MHz. The underlying reason for this is, as in the dilution study, not a dynamical but a shielding effect.

We believe that the reason for these observations, based solely on the present NMR study, is a matter of speculation. It is, however, plausible to suggest that various degrees of molecular association or short-range molecular ordering are the basis of these interesting shielding effects.

Acknowledgment. We wish to thank Professor W. H. Urry, University of Chicago, for the 270-MHz spectra and stimulating discussions, and R. E. Miller for experimental work.

Registry No.—I, 930-38-1.

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A Novel Synthesis of Trifluoromethylthioacetic Acid

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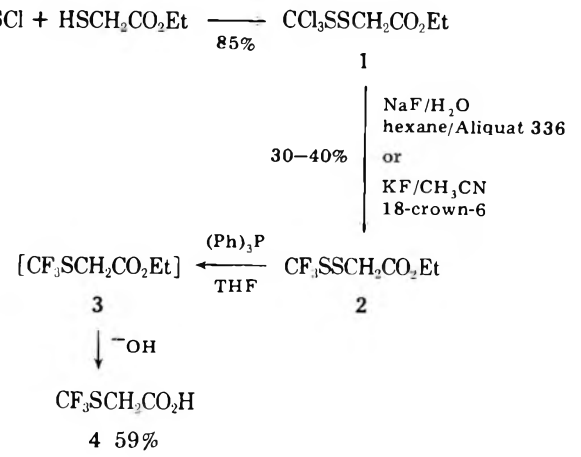
The synthesis of trifluoromethylthioacetic acid,[1,2] an important intermediate in the preparation of the semisynthetic cephalosporin antibiotic cefazaflur (SKF 59962),[3] is made difficult by the limited methods available for the elaboration of the trifluoromethylthio moiety.[4] We wish to report a facile route to this compound from ethyl mercaptoacetate which provides a potentially useful method for the conversion of thiols to trifluoromethyl sulfides.

Chlorination of a methyl group adjacent to sulfur followed by halogen exchange with an inorganic fluoride at elevated temperature is one of the most widely used methods for the synthesis of a trifluoromethylthio group.[5] Thus, our initial approach to the synthesis of trifluoromethylthioacetic acid was to prepare the corresponding trichloride and convert it by existing methods to the trifluoride. However, in methylthioacetic acid the methylene adjacent to the sulfur is sufficiently activated by the carboxyl group to preclude selective chlorination of the methyl.

As an alternate approach we tried fluorination of the readily available disulfide 1, followed by sulfur extrusion to give an ester of trifluoromethylthioacetic acid. Although the fluoride exchange could not be carried out by the usual method, i.e., antimony trifluoride–antimony pentachloride, we discovered that it occurred rapidly under mild conditions using phase transfer catalysis. Treatment of a hexane solution of 1, pre-

pared by condensing trichloromethylsulfenyl chloride with ethyl mercaptoacetate, with a twofold excess of aqueous sodium fluoride at room temperature in the presence of a catalytic amount of Aliquat 336[6] gave the trifluoro disulfide **2** in 35% yield. Alternatively, addition of **1** to a cold suspension of



potassium fluoride in acetonitrile containing a catalytic amount of 18-crown-6 also yielded **2** (41%). To our knowledge this represents one of the first examples of a phase-transfer mediated trisubstitution of fluorine for chlorine, and it occurs under unusually mild conditions.[7-9] Treatment of disulfide **2** with an aminophosphine[10] resulted in an extremely exothermic reaction which produced only traces of sulfide **3**. However, when disulfide **2** was added to a THF solution of triphenylphosphine it was smoothly desulfurized to **3**. With one recent exception[11] reports of desulfurizations of disulfides with triphenylphosphine had been limited to acyl or vinylogous disulfides.[12] In the present case, the extremely electronegative trifluoromethyl group may polarize the disulfide sufficiently to render it labile to attack by triphenylphosphine. Since ester **3** was difficult to isolate in good yield because of its tendency to codistill with a variety of solvents, it was hydrolyzed in situ with 5% sodium hydroxide to produce pure trifluoromethylthioacetic acid in 59% yield (from **2**).

Experimental Section

Infrared spectra were obtained in $CHCl_3$ using a Perkin-Elmer Infracord; NMR spectra were obtained in $CDCl_3$ on a Varian T-60 spectrometer using Me_4Si as an internal standard; VPC analyses were carried out on a F & M 700 gas chromatograph with a 6 ft SE-30 column. $MgSO_4$ was used as drying agent for organic extracts.

Ethyl Trichloromethyldithioacetate (1). Ethyl mercaptoacetate (36 g, 0.3 mol) was added dropwise with stirring over 1 h to trichloromethylsulfenyl chloride (55.8 g, 0.3 mol). The mixture was stirred at room temperature for an additional 1 h and then distilled to yield 69 g (85%) of **1** as a pale yellow oil: bp 94–96 °C (0.3 mm); NMR δ 4.20 (q, 2, J = 7 Hz), 3.90 (s, 2), 1.35 ppm (t, 3, J = 7 Hz); IR 1725, 845 cm^{-1}. Anal. Calcd for $C_5H_7Cl_3O_2S_2$: C, 22.28; H, 2.62; Cl, 39.45. Found: C, 22.68; H, 2.67; Cl, 39.83.

Ethyl Trifluoromethyldithioacetate (2). A. A mixture of 30 mL of hexane containing 5.40 g (20 mmol) of disulfide **1** and 30 mL of H_2O containing 5.04 g (120 mmol) of NaF was stirred at room temperature while about 0.7 g of Aliquat 336 in 1 mL of hexane was added. After stirring at room temperature overnight the mixture was diluted with 100 mL of hexane and the organic layer separated, washed with H_2O, dried, filtered, and evaporated. The residue was distilled under aspirator pressure to give 1.4 g (35%) of **2** as a pale yellow liquid: bp 72–74 °C (10 mm); NMR δ 4.24 (q, 2, J = 7 Hz), 3.72 (s, 2), 1.30 ppm (t, 3, J = 7 Hz); IR 1725, 1145 cm^{-1}; m/e M^+ 220.

B. To an ice-cold solution of 1.6 g (6 mmol) of 18-crown-6 in 50 mL of dry CH_3CN was added 7.0 g (120 mmol) of KF and the suspension stirred for 30 min. To this rapidly stirred solution was added dropwise over ~20 min a solution of 5.4 g (20 mmol) of disulfide **1** in 10 mL of CH_3CN. The mixture was stirred in the cold for an additional 1 h and then at room temperature for 2 h. Suspended solids were removed by filtration and the filtrate was evaporated. The residue was triturated with petroleum ether and filtered and the filtrate was concentrated and distilled to give 1.8 g (41%) of **2** as a light tan oil.

Trifluoromethylthioacetic Acid (4). The disulfide **2** (4.4 g, 20 mmol) dissolved in 20 mL of THF was added dropwise to a stirred solution of 5.8 g (22 mmol) of triphenylphosphine in 50 mL of THF. After addition was complete, the mixture was stirred at room temperature for 30 min. An additional 1 g of triphenylphosphine was added in 0.5-g portions and stirring continued for 15 min longer until VPC indicated complete consumption of starting material. Fifty milliliters of 5% NaOH was added and the mixture stirred rapidly for 1 h. Most of the THF was removed under vacuum and the mixture diluted with 200 mL of H_2O. It was washed twice with benzene and twice with Et_2O, acidified to pH 1.5 with 3 N HCl, and extracted with three portions of Et_2O. The latter extracts were combined, dried, filtered, and evaporated to give a brown oil which was distilled to give 1.9 g (59%) of **4** as a pale yellow oil: bp 87–88 °C (11 mm) [lit.[1] 101 °C (31 mm)]; NMR δ 10.25 (s, 1), 3.80 ppm (s, 2); IR 1710, 1240 cm^{-1}.

Registry No.—**1**, 61915-55-7; **2**, 61915-56-8; **4**, 2408-17-5; ethyl mercaptoacetate, 623-51-8; trichloromethylsulfenyl chloride, 594-42-3.

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(8) The remarkable ease of this substitution might be accounted for by an initial sulfur–sulfur bond cleavage followed by halogen exchange to produce a trifluoromethylsulfenyl halide which could then recombine with ethyl mercaptoacetate producing **3**. Tullock and Coffman [(*J. Org. Chem.*, **25**, 2016 (1960)] report the conversion of trichloromethylsulfenyl chloride to trifluoromethylsulfenyl chloride with sodium fluoride in hot tetramethylene sulfone. Trifluoromethylsulfenyl chloride readily combines with thiols to give disulfides.
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Neighboring Sulfide Group in Thermal Decomposition of Aryldiazonium Salts

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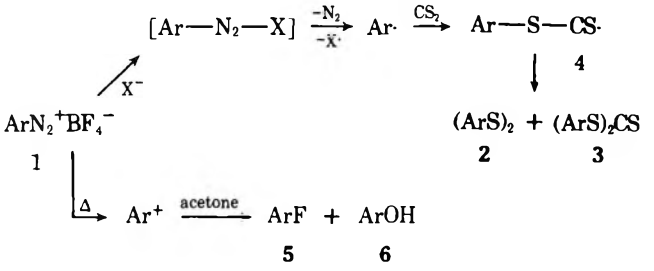
Aryldiazonium tetrafluoroborates (**1**) are a well-known source of aryl radicals when they undergo reduction by nucleophilic species.[1] The mechanism proposed[2] involves the attack of nucleophilic species at the β nitrogen of the diazonium group to form an intermediate which then fragments homolytically, releasing X·, N_2, and aryl radicals. Recently, we studied[3] this reaction in carbon disulfide and we found that this solvent is a good scavenger for aryl radicals, which add to the carbon–sulfur double bond to give diaryl disulfide (**2**) and diaryl trithiocarbonate (**3**) through an intermediate arylthiothiocarbonyl radical (**4**). Otherwise, the thermal decomposition of **1** gives the aryl cation.[4] When the reaction was carried out in acetone, fluoroarenes (**5**) and phenols (**6**) were obtained;[4] no addition products on the carbon–sulfur double

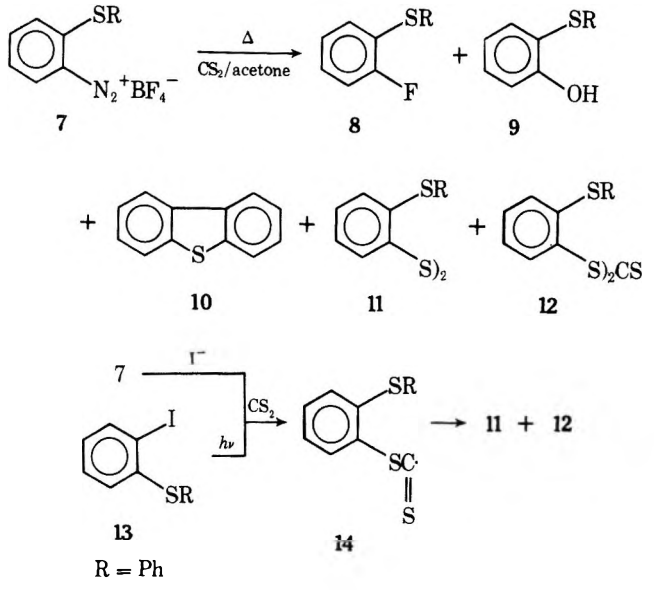
bond were isolated when the thermal decomposition was carried out in the presence of carbon disulfide (Scheme I).

Scheme I



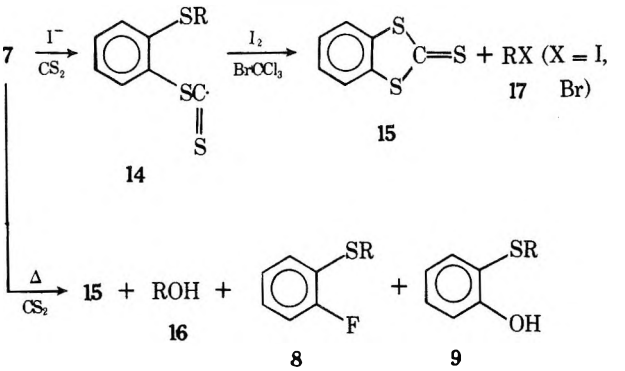
We now wish to report the thermal decomposition of *o*-aryl- and *o*-alkylthioaryldiazo tetrafluoroborates in carbon disulfide and discuss the influence of neighboring sulfide group on the reaction mechanism. When *o*-phenylthiobenzenediazonium tetrafluoroborate (**7**, R = Ph) was heated at 45 °C for 24 h in an acetone/carbon disulfide mixture, we obtained, besides 2-fluorodiphenyl sulfide (**8**, R = Ph) and 2-hydroxydiphenyl sulfide (**9**, R = Ph), dibenzothiophene (**10**), bis-*o*-phenylthiophenyl disulfide (**11**, R = Ph), and di-*o*-phenylthiophenyl trithiocarbonate (**12**, R = Ph). Compounds **11** and **12** were also obtained by reduction of **7**, R = Ph, with iodide ions or by photolysis of 2-iododiphenyl sulfide (**13**, R = Ph) in carbon disulfide, through the radical (**14**, R = Ph) as intermediate (Scheme II).

Scheme II



From thermal decomposition of tetrafluoroborate **7**, R = n-$C_{12}H_{25}$, benzo-1,3-dithiol-2-thione (**15**) and 1-dodecanol (**16**) were formed together with *o*-fluorophenyl *n*-dodecyl sulfide (**8**, R = n-$C_{12}H_{25}$) and *o*-hydroxyphenyl *n*-dodecyl sulfide (**9**, R = $C_{12}H_{25}$); formation of **11** and **12** was not observed in this case. Moreover, reduction of **7**, R = n-$C_{12}H_{25}$, gave compound **15** and iodododecane (**17**, R = n-$C_{12}H_{25}$; X = I) and no trace of **11**, R = n-$C_{12}H_{25}$, and **12**, R = n-$C_{12}H_{25}$; on the other hand, addition of bromotrichloromethane to the reaction mixture led to small amounts of bromododecane (**17**, R = n-$C_{12}H_{25}$; X = Br) (Scheme III). Formation of **15** in this reaction is in agreement with what was previously reported[3] on the reduction of **7**, R = CH_3, in carbon disulfide, and could be rationalized by assuming that the radical **14**, R = n-$C_{12}H_{25}$, instead of undergoing the usual reaction leading to **11** and **12**, prefers to undergo intramolecular homolytic addition on the

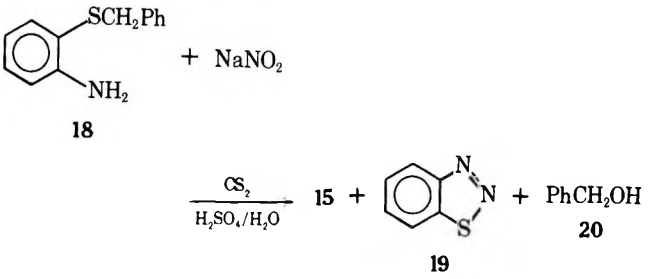
Scheme III



R = $C_{12}H_{25}$

sulfur atom of the ortho alkylthio group, followed by loss of a dodecyl radical which can be trapped by iodine or bomotrichloromethane. However, this route appears to be different from that observed with **7**, R = n-$C_{12}H_{25}$, which gives **15** by thermal decomposition; formation of **16** would suggest that in this case dodecyl cations, rather than dodecyl radicals, are displaced, thus indicating that the reaction intermediate must be different from **14**. Attempts to obtain the tetrafluoroborate **7**, R = $PhCH_2$, were not successful because the diazotization of 2-aminophenyl benzyl sulfide (**18**) led very rapidly to 1,2,3-benzothiadiazole (**19**) and benzyl alcohol (**20**);[5,6] however, when the diazotization of **18** was carried out in a mixture of sulfuric acid/carbon disulfide, we obtained traces of **15** as well as **19** and **20** (Scheme IV).

Scheme IV



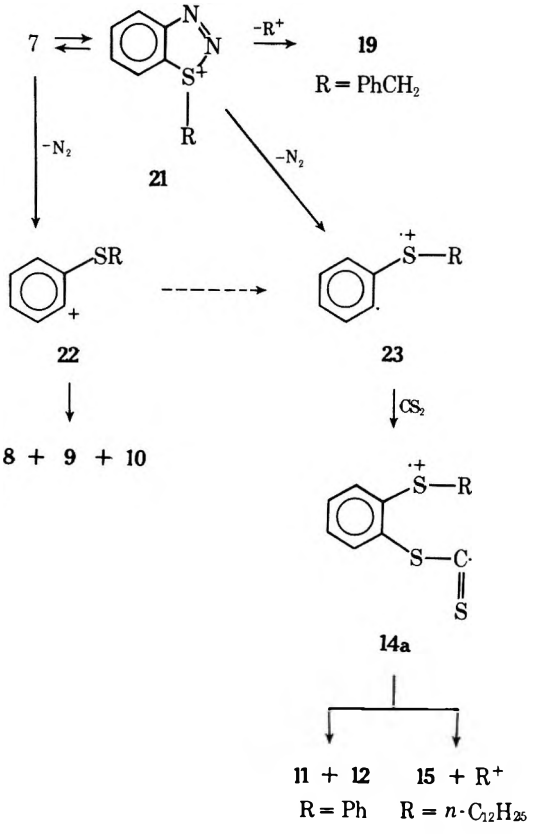
All these results appear to offer evidence of participation of the neighboring sulfur atom in the thermal decomposition of diazonium salts; a plausible mechanism could be a nucleophilic attack by the sulfur atom on the β nitrogen of the diazonium group, to afford a benzodiazothiolium salt (**21**) in equilibrium with the "open" diazonium salt **7**; in fact **7**, by nitrogen loss, can lead to the aryl cation (**22**), from which products **8**, **9**, and **10** are formed. Two kinds of reactions seem to be possible for intermediate **21**: loss of R^+ leading to **19**, when R^+ is a stable cation such as the benzyl cation, or nitrogen loss giving the radical intermediate **23**. By reaction with carbon disulfide, radical **23** would then form the radical **14a**, from which products **11** and **12**, when R = Ph, and **15**, when R = alkyl, can be produced (Scheme V).

Another possible route leading to **23** could be an intramolecular charge transfer process from cation **22**. This alternative mechanism can be ruled out at least in one case investigated; in fact, the thermal decomposition of **7**, R = CH_3, afforded **15**, but no traces of **8**, R = CH_3, and **9**, R = CH_3. These results appear to exclude the formation of aryl cation **22**, R = CH_3, and thus the formation of **23** by a charge transfer process.

Experimental Section

GLC analyses were carried out with a Varian 1440/1 instrument (5% FFAP on a Varaport column). The reaction products were identified, when possible, by mixture melting points with prepared authentic

Scheme V



specimens, and by comparison of their IR spectra (Perkin-Elmer 257), or by low-resolution mass spectral analysis (JEOL JMS D100). Aryldiazonium tetrafluoroborates were all prepared from parent diazotizated amines, as described by Hey and co-workers.[7] Dibenzothiophene (**10**), dodecanol (**16**), iodo- and bromododecane, benzyl alcohol (**19**), and 2-aminobiphenyl are commercial products.

2-biphenylylol,[8] 2-fluorobiphenyl,[9] 2-hydroxydiphenyl sulfide (**9**, R = Ph),[10] bis-o-phenylthiophenyl disulfide (**11**, R = Ph),[11] 2-iododiphenyl sulfide (**13**),[12] benzo-1,3-dithiol-2-thione (**15**),[13] 1,2,3-benzothiadiazole (**19**),[14] 2-aminodiphenyl sulfide,[15] o-methylthioaniline,[16] and *o*-aminophenyl benzyl sulfide (**18**)[17] were prepared as described in the literature. Carbon disulfide was dried with calcium chloride and then distilled twice. Acetone was refluxed over $KMnO_4$ and distilled over P_2O_5 twice.

***o*-Aminophenyl *n*-Dedecyl Sulfide.** A solution of *o*-chloronitrobenzene (16 g, 0.1 mol) and sodium *n*-dodecylthiolate (22 g, 0.1 mol) in methanol (200 mL) was refluxed for 3 h, then poured in cold water. The o-nitrophenyl *n*-dodecyl sulfide obtained was extracted with ethyl ether and purified by chromatography on a silica gel column, yield 80%, mp 34 °C. Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04; N, 4.33; S, 9.91. Found: C, 66.84; H, 8.99; N, 4.39; S, 9.96. The nitro derivative was reduced over palladium/charcoal in dichloromethane. Filtration, evaporation, and distillation gave the title product (22 g) as an oil. Anal. Calcd for $C_{18}H_{31}NS$: C, 73.66; H, 10.65; N, 4.77; S, 10.92. Found: C, 73.78; H, 10.68; N, 4.82; S, 11.04.

Thermal Decomposition of Aryldiazonium Tetrafluoroborates. The salt (0.005 mol) was dissolved in acetone (20 mL) and carbon disulfide (15 mL) was added; this solution was heated at 45 °C for 24 h. After this time, the fluoroborate was all decomposed (negative test with β-naphthol). The reaction mixture was then analyzed by GLC and/or chromatographed on a silica gel column.

A. From 1, Ar = *o*-PhPh. By column chromatography of the reaction mixture 2-fluorobiphenyl (12%) and 2-biphenylylol (85%) were separated.

B. From 7, R = Ph. The following products were separated: 2-fluorodiphenyl sulfide (**8**, R = Ph, 12%) [bp 142 °C (16 mm). Anal. Calcd for $C_{12}H_9FS$: C, 70.56; H, 4.44; F, 9.30; S, 15.70. Found: C, 70.0; H, 4.49; F, 9.51; S, 15.58. Mass spectrum *m/e* 204 (M^+·, 100), 185 (17), 184 (12).]; 2-hydroxydiphenyl sulfide (**9**, R = Ph, 22%); dibenzothiophene (**10**, 3%); bis-*o*-phenylthiophenyl disulfide (**11**, R = Ph, 17%); di-2-phenylthiophenyl trithiocarbonate (**12**, R = Ph, 14%) [mp 113 °C. Anal. Calcd for $C_{25}H_{18}S_5$: C, 62.73; H, 3.78; S, 33.49. Found: C, 62.7; H, 3.74; S, 33.39. Mass spectrum *m/e* 478 (M^+·,1.5), 434 (0.3), 369 (92), 293 (7), 261 (100), 229 (28), 228 (35), 217 (35), 21 (40), 185 (65), 184 (85).].

C. From 7, R = $C_{12}H_{25}$. The reaction mixture was analyzed by GLC, and *n*-dodecanol was identified. Then, from column chromatography, it was separated: *o*-fluorophenyl *n*-dodecyl sulfide (**8**, R = $C_{12}H_{25}$, 14%) [bp 144 °C (16 mm). Anal. Calcd for $C_{18}H_{29}FS$: C, 72,92; H, 9.86; F, 6.41; S, 10.81. Found: C, 72.88; H, 9.81; F, 6.26; S, 10.94. Mass spectrum *m/e* 296 (M^+·, 92), 128 (100).]; *o*-hydroxyphenyl *n*-dodecyl sulfide (**9**, R = $C_{12}H_{25}$, 25%) [bp 122 °C (1 mm). Anal. Calcd for $C_{18}H_{30}OS$: C, 73.41; H, 10.27; S, 10.89. Found: C, 73.35; H, 10.21; S, 10.81. Mass spectrum *m/e* 294 (M^+·, 100), 126 (80).]; benzo-1,3-dithiol-2-thione (**15**, 30%).

D. From 7, R = CH_3. Only benzo-1,3-dithiol-2-thione (**15**, 35%) was separated from column chromatography, together with other heavy products not identified. No o-methylthiofluorobenzene and o-methylthiophenol were found.

Reduction of Aryldiazonium Tetrafluoroborates with Iodide Ions. The salt (0.005 mol) was dissolved in an acetone (15 mL)/carbon disulfide (15 mL) mixture under stirring. Sodium iodide (0.8 g) was added slowly and, after nitrogen evolution, the mixture was refluxed for 0.5 h. It was then poured in water and the organic layer separated. The crude obtained by solvent evaporation was chromatographed on a silica gel column.

A. From 7, R = Ph. *o*-Iododiphenyl sulfide (3.3%), bis-o-phenylthiophenyl disulfide (**11**, R = Ph, 46%), and di-*o*-phenylthiophenyl trithiocarbonate (**12**, R = Ph, 33%) were obtained.

B. From 7, R = *n*-$C_{12}H_{25}$. This reaction was carried out in the presence of bromotrichloromethane (0.01 mol). From column chromatography iodododecane (37%), little amounts of bromododecane (detected by GLC/MS), and benzo-1,3-dithiol-2-thione (**15**, 53%) were separated. GLC analysis of the reaction mixture showed that 1-dodecanol was not present. No addition products of *n*-dodecyl radical on carbon disulfide were isolated.

Photolysis of 2-Iododiphenyl Sulfide (13). A solution of **13** (0.56 g, 0.002 mol) in carbon disulfide (3 mL) and ethyl ether (7 mL) mixture was photolyzed using a low-pressure mercury lamp Hanau Type P.L. 369 for 18 h. By column chromatography of the reaction mixture on silica gel, unreacted starting product (0.27 g), bis-o-phenylthiophenyl disulfide (**11**, R = Ph, 44%), and di-o-phenylthiophenyl trithiocarbonate (**12**, R = Ph, 35%) were separated.

Diazotization of o-Aminophenyl Benzyl Sulfide (18). The amine **18** (3.6 g) was suspended in a cold solution of concentrated H_2SO_4 (3 mL) in water (15 mL) and carbon disulfide (15 mL) was then added. To this mixture a solution of $NaNO_2$ (1.3 g) in water (5 mL) was added dropwise, under vigorous stirring, at 0–5 °C. After addition, the mixture was stirred for 0.5 h at 10–20 °C, and then warmed at 45 °C until the test with β-naphthol was negative. The organic layer was separated and the solvent evaporated. By column chromatography of the crude on silica gel with carbon disulfide as eluent, benzo-1,3-dithiol-2-thione (**15**, traces), 1,2,3-benzothiadiazole (**19**, 95%), and benzyl alcohol (**20**, 75%) were separated.

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Registry No.—**1** (AR = o-PhPh), 318-13-8; **7** (R = Ph), 59014-91-4; **7** (R = $C_{12}H_{25}$), 61900-50-3; **7** (R = CH_3), 52959-17-8; **8** (R = Ph), 61900-51-4; **8** (R = $C_{12}H_{25}$), 61900-52-5; **9** (R = $C_{12}H_{25}$), 61900-53-6; **12** (R = Ph), 61900-54-7; **13**, 2236-42-2; **18**, 6325-92-4; *o*-aminophenyl *n*-dodecyl sulfide, 61900-55-8; *o*-chloronitrobenzene, 88-73-3; sodium *n*-dodecylthiolate, 26960-77-0; *o*-nitrophenyl *n*-dodecyl sulfide, 61900-56-9.

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Addition of Bisulfite to Cytosine Derivatives[1]

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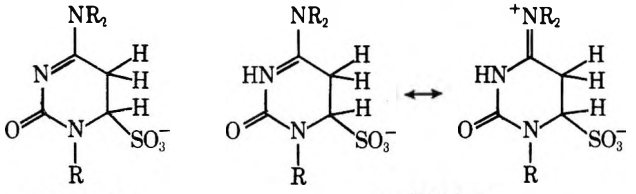
Studies of nucleophilic addition at the 5,6 double bond of pyrimidines with water,[2-4] alcohols,[5] bromine water,[6,7] hydroxylamines,[8,9] bisulfite,[10,11] etc.,[12] are essential in understanding chemical modifications of biologically active nucleic acids that may cause mutation and thus constitute a genetic hazard. The molecular structures of Ura addition products (such as photohydrates) were well established in 1956,[13] but actual isolation of Cyt addition products remains to be achieved.[14,15] Because of our interest in Cyt photohydrates[16] and because the Cyd bisulfite addition product has been isolated,[10,11] we prepared several Cyt bisulfite addition products. The UV absorption spectra for these compounds were measured, and IR and NMR spectra were obtained. This information should be valuable in bisulfite addition reactions, photohydration, and similar nucleophilic additions of Cyt derivatives.

Results and Discussion

In connection with our study of the chemistry of photodimerization of Cyt derivatives,[17] a series of methyl derivatives was prepared. It is advantageous to study these derivatives because $N(1)$-Me derivatives are analogues of biologically active compounds and $N(4)$-Me derivatives may provide information relating to the nature of amino–imino tautomerization of C(4)-NH_2 moiety in hCyt compounds.

Using a general procedure,[10,11] hCyt 6-sulfonate derivatives were obtained in yields varying from 20 to 95% (Table IA). Because adequate amounts could be obtained for our studies, no attempts were made to improve the product yields.

Table IB shows UV absorption spectral data of these compounds in aqueous solutions. The monoanions, as shown, probably exist in solutions with pH >9 (also see later discussion). The N^1-Me group causes an auxochromic shift of 3–4 nm in λ_{max} with a slightly higher ϵ_{max} that is consistent with that observed in hCyt [λ_{max} (pH 8) 239 nm] and Me^1hCyt [λ_{max} (pH 8) 243 nm].[18] N^4-Methylation produces more pronounced bathochromic shifts of >10 nm as seen in Me^1, $Me_2^{1,4}$, and $Me_3^{1,4,4}$ derivatives. A similar shift was reported in 1-cyclohexyl-hCyt [λ_{max} (pH 8) 245 nm] and 1-cyclohexyl-$Me_2^{4,4}$hCyt [λ_{max} (pH 8) 258 nm].[18,19]



monoanion zwitterion

In water (pH ~5), these addition products either exhibit λ_{max} <220 nm or end absorption with shoulders in the 240–260-nm regions. Characteristics of the former are analogous to those of hUra derivatives.[20] The position of the latter depends on the extent of N(4)-methylation, but their intensities are much reduced as compared to those observed at pH >9. This hypochromic effect indicates that monoanions are no longer the only or preponderant form under this condition. The appearance of strong absorption in the 220-nm region suggests that molecules with an exocyclic C=N bond exist predominantly for these bisulfite addition products because the predominant form of hUra compounds has the exocyclic C=O bonds and exhibits end absorptions. This could result from the amidinium resonance by protonation at N(3) in a zwitterion as shown.

Ionization constants of these compounds were estimated

Table I. Preparations and Ultraviolet Spectral Data of 5,6-Dihydrocytosine 6-Sulfonate Derivatives

	Methyl derivatives of cytosine					Nucleoside, Cyd
	1-	1,4-	4,4-	1,4,4-	4,5-	
			A. Preparation Conditions			
Amount, mmol	1.0	2.0	1.0	1.0	1.0	1.5
[in HOH, mL]	[1.5]	[1.0]	[0.5]	[No]	[2.0]	[No]
HSO_3^-, mmol	6.0	12.0	3.0	3.0	6.0	9.0
[in HOH, mL]	[1.0]	[2.0]	[0.7]	[0.7]	[1.0]	[1.8]
Time, ~day	1	2	1	2	4	1
Yield, ~%	60	95	20	70	80	37
Mp, °C	>280	176	207	149	202	205
			B. Ultraviolet Spectral Data			
Zwitterion (pH 5.1)						
λ_{max}, nm	217	217	221	222	218	218
$\epsilon_{max} \times 10^{-3}$	3.9	5.7	5.2	7.6	5.5	5.1
λ_{sh}, nm	242	238	255	260		241
$\epsilon_{sh} \times 10^{-3}$	2.6	3.9	2.1	3.0		3.6
Monoanion (pH 9.9)						
λ_{max}, nm	243	251	258	262	248	246
$\epsilon_{max} \times 10^{-3}$	8.3	9.5	8.1	9.9	8.0	8.5
λ_{min}, nm	229	233	234	238	229	230
$\epsilon_{min} \times 10^{-3}$	7.9	5.5	3.9	4.6	5.5	6.7
pK_a	~5.6	~5.7	~5.6	~5.7	~5.6	~5.4
λ_{aw}, nm	248	250	257	261	246	245

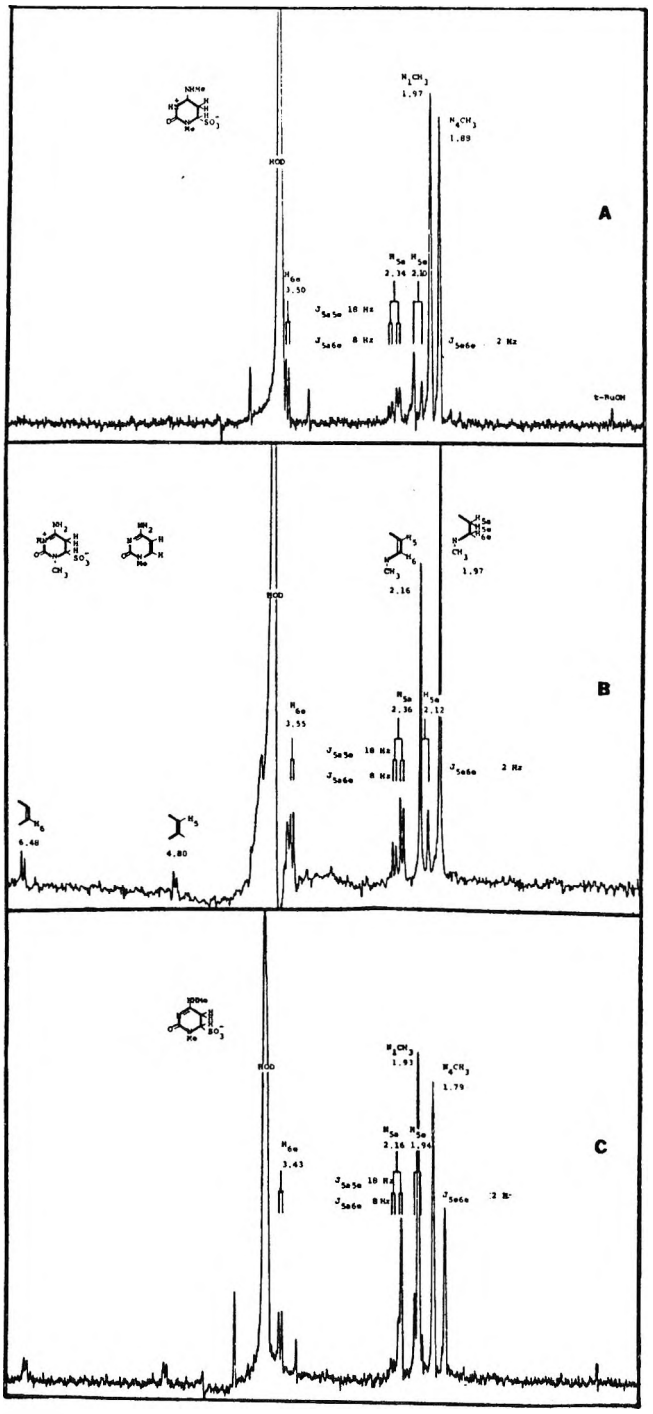


Figure 1.

spectroscopically. First, preliminary experiments were carried out to determine the stability of these bisulfite addition products under the pH titration conditions. Second, the choice of an analytical wavelength (λ_{aw}), at which the two species differ most in optical density from one another, was made for each compound. They are listed in Table IB and were used for the determinations. The pK_a values were calculated according to the normal method[21] and are given also in Table IB. These values, ranging from 5.4 to 5.7, are comparable to that of Cyd hydrate[4] and are somewhat lower than those of hCyt derivatives.[18] These correspondences argue for the validity of these estimated pK_as despite the slight instability of these compounds at a higher pH which, of course, precludes assay of precise pK_a values. The values of p$K_a \sim 6$ imply that the UV spectra at pH ~10 are those of monoanionic and at pH ~5, a mixture of monoanionic and zwitterionic.

In further confirming the molecular structures of these bisulfite addition products, NMR studies of these compounds were made. Similar spectral patterns were seen for all compounds but the characteristic bands of parent compounds were also weakly displayed by some because of a slight reversion to original compounds. The spectra of two representative compounds, one methylated and the other unmethylated at N(4), are illustrated in Figure 1 showing the assignments, chemical shifts (δ), and coupling constants (J). Figure 1A shows the spectrum of a zwitterionic species of Me_2[1,4]hCyt 6-sulfonate because the saturated solution was found to have a pH of 3.9. A pattern of ABX for $H_{5ax}H_{5eq}H_{6eq}$ is clearly discernible. While the signal of H_{5eq} appears as a doublet, the H_{5ax} exhibits a quartet. This variance occurs because the vicinal proton–proton coupling constant is very small for $H_{5eq}H_{6eq}$. The low solubility and instability of these compounds did not allow sufficient data acquisition time to show a splitting with $J \leq 2$ Hz using a 220-MHz spectrometer. (This was measured as 2 Hz with a 100-Mhz spectrometer.) This small coupling constant is best attributed to a 1,2-trans diequatorial coupling[22] and indicates that the sulfonate group occupies the 6-axial position.[10,11] Figure 1B shows the spectrum of Me[1]hCyt 6-sulfonate and a similar ABX pattern is discernible. In addition, weak signals of Me[1]Cyt are also displayed. Figure 1C shows the NMR spectrum of the monoanion of Me_2[1,4]hCyt 6-sulfonate. While the pattern and the couplings remain the same as in the zwitterion, the expected upfield shifts of 0.12, 0.20, and 0.18 ppm for H_{6eq}, H_{5ax}, and H_{5eq}, respectively, are evident. These larger magnitudes of $\Delta\nu$ for the C(5) protons probably indicate that protonation occurs at N(3) for the corresponding zwitterion.

These findings should add to the knowledge of the addition of bisulfite to pyrimidines, which has considerable importance in nucleic acid chemistry and biology.[23–26]

Experimental Section

Addition of Bisulfite to Cytosine Derivatives. The method of preparing these addition products is essentially the same.[10,11] The pulverized Cyt derivative was added directly or was dissolved first in a minimal volume of water before it was added to a cold solution of sodium bisulfite. Total volume was also kept minimal to aid crystallization from the reaction mixture that was stirred at ~5 °C and then allowed to stand in the refrigerator. The deposited crystals were collected by filtration, washed twice with cold water (0.5 mL) and thrice with methanol (1 mL), and dried under vacuum. Reaction conditions are shown in Table IA.

Determination of Ultraviolet Spectra of 5,6-Dihydrocytosine 6-Sulfonate Derivatives. A preliminary experiment was conducted for each bisulfite addition product. This was effected by dissolving ~1 mg of the compound in 50 mL of water cooled in an ice bath (~5 °C). The solution was titrated to pH ~10 by the addition of cold 0.01 N KOH solution. Then at 1-min intervals, UV spectra were recorded. The increase of the ϵ_{max} was found to be less than 3% in a 5-min interval, which is slower than that observed for the regeneration of Cyd from the Cyd–bisulfite addition product ($t_{1/2}$ 6 min) at a higher temperature (13 °C).[11] Also, the choice of the analytical wavelengths was made.

The determination of the pK_a value was made with 250 mL of a 1×10^{-4} M aqueous solution of the compound. The solution was kept at ~5 °C with stirring during titration. The optical densities at the λ_{aw} were recorded as soon as equilibrium was reached at pH ~10. Then a reading was taken when the solution was adjusted to pH ~7 with HCl. Adjustments between pH ~7 and ~4 were made in nine or ten steps, each resulting in a 0.3–0.5 pH change. The OD at λ_{aw} were recorded at each step and their corresponding pHs were accurately determined. A combination of 0.01, 0.1, and 1 N HCl was used to minimize the volume change of the solution. The OD at λ_{aw} of the solution at pH ~10 and pH ~3 were assigned for the monoanion (OD_M) and the zwitterion (OD_Z), respectively.

Nuclear Magnetic Resonance Spectra of Me_2[1,4]-hCyt and Me[1]-hCyt 6-Sulfonate. These spectra were obtained with a Varian HR 220-MHz spectrometer by Dr. G. McDonald of the Johnson Foundation at the University of Pennsylvania. They were taken at 5 °C in D_2O using *tert*-butyl alcohol as an internal standard.

Registry No.—Sodium bisulfite, 7631-90-5; 1-methylcytosine, 1122-47-0; 1,4-dimethylcytosine, 6220-49-1; 4,4-dimethylcytosine, 6220-48-0; 1,4,4-trimethylcytosine, 2228-27-5; 4,5-dimethylcytosine, 62006-34-2; 1-methyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-35-3; 1,4-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-36-4; 4,4-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-37-5; 1,4,4-trimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-05-7; 4,5-dimethyl-5,6-dihydrocytosine-6-sulfonic acid, 62006-06-8; sodium 1-methyl-5,6-dihydrocytosine-6-sulfonate, 62006-07-9; sodium 1,4-dimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-08-0; sodium 4,4-dimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-09-1; sodium 1,4,4-trimethyl-5,6-dihydrocytosine-6-sulfonate, 62006-10-4; sodium 4,5-dimethyl-5,6-dihydrocytosine-6-sulfonate 62029-61-2; 5,6-dihydrocytidine-6-sulfonic acid, 29725-37-9; sodium 5,6-dihydrocytidine-6-sulfonate, 62006-11-5.

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Coordinative Role of Alkali Cations in Organic Reactions. 1. Selective Methylation of the Alcoholic Group of Kojic Acid

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There is no method in the literature which describes methylation of an alcoholic group of an organic compound in the presence of its phenolic group. Kojic acid, 5-hydroxy-2-hydroxymethyl-γ-pyrone (HkH), can be methylated to 5-methoxy-2-hydroxymethyl-γ-pyrone (MkH) with diazomethane[1,2] or by treating a 1:1 mixture of HkH and KOH with a stoichiometric amount of dimethyl sulfate (DMS).[3] Both the hydroxyl groups of HkH can be methylated using an excess of KOH and DMS[2,4] to produce MkM.

There is no rationalized method of methylating HkH to obtain 5-hydroxy-2-methoxymethyl-γ-pyrone (HkM). However, the latter is reported[5] produced along with MkM when an aqueous solution of HkH (1 mol) and KOH (6 mol) is treated with DMS (3.7 mol). We feel that HkM is produced in this reaction because the amount of KOH overweighs that of DMS and the phenoxy site gets protected against the incipient CH_3^+ by K^+. This suggested to us the synthesis of HkM employing an excess of LiOH as alkali for a 1:1 reaction mixture of HkH and DMS. It was found that a threefold excess of LiOH could perfectly protect the phenoxy site (through the formation of partly covalent lithium kojate, $Li^+ {}^-kH$) in water against a stoichiometric amount of DMS at and below 40 °C.

Synthesis of HkM. Take 2.84 g (0.01 mol) of HkH and 2.60 g (0.03 mol) of $LiOH \cdot H_2O$ in 15 mL of water and maintain the reaction mixture at 35–40 °C. Add dropwise 1.7 mL (0.013 mol) of DMS in about 20 min while stirring constantly. Keep the reaction mixture for 30 min and add 2 N HCl to pH 6 and evaporate the solution to a semisolid employing a rotary evaporator. Extract HkM with six lots (10 mL) of benzene and crystallize it by expelling the latter at room temperature, yield ca. 55% (mp 72–74 °C, lit. mp 75–76 °C). The product can be recrystallized from ethyl acetate.[5]

Below 35 °C the reaction appears to be too slow whereas at 35–40 °C a fraction of DMS gets destroyed owing to alkali present in excess. Consequently, the yield of HkM is promoted by using a slight excess of DMS at 35–40 °C; DMS exceeding the recommended amount favors the formation of MkM. The product and an authentic sample of HkM both give a red color with ferric chloride. Infrared spectra of both show a broad band at 3300 cm^{-1} indicative of a free phenolic hydroxyl group ($-CH_2OH$ of HkH and MkH absorbs at about 3200 cm^{-1}). ^1H NMR spectra (80 MHz in D_2O) of both show an absorption at 2.7 ppm which is characteristic of the $-CH_2OCH_3$ methyl protons ($-OCH_3$ protons of MkH and MkM produce a singlet around 3 ppm).

Discussion

Methylation of $-CH_2OH$, obviously, is due to coordination of this group with Li^+, for this aids polarization of the alcoholic proton and its elimination with OH^-. The resulting oxide directly associates with the incipient CH_3^+ instead of Li^+ to produce $-CH_2OCH_3$. If ion pairing of the oxide with Li^+ should have taken place preferentially then conversion of $-CH_2OLi$ to $-CH_2OCH_3$ should have not been possible, for Li^+ cannot be replaced with CH_3^+ even from the more delocalized phenoxy site under these conditions as seen from the possibility of obtaining HkM. The idea of coordination of Li^+ derives its justification from the fact that even the low charge density K^+ and Cs^+ have been found to be coordinated (x-ray analysis) to $-CH_2OH$ in the compounds KI (phenacyl kojate)$_2$[6] and CsNCS(phenacyl kojate),[7] respectively.

Previous workers[5] failed to obtain the dienol by opening the γ-pyrone ring of HkH; we note that HkH and HkM do not undergo ring opening. This is probably because electron depletion (and hence bond weakening) of the ring through the carbonyl oxygen is overcompensated by the electron supply from the phenoxide created by the alkali. This should be true, in principle, for any γ-pyrone ring carrying an ionizable hydroxyl group.

The $Ar(OH)(CH_2OH)$ type of compounds, which do not polymerize in alkaline medium, should in principle be methylated selectively. Optimum conditions may be discovered by keeping in view that (1) methylation of the alcoholic group is favored as the DMS/substrate ratio exceeds 1 and the temperature of the reaction is raised (toward 50 °C), and (2) methylation of the phenolic group, which takes place via salification, can be prevented when LiOH/DMS and LiOH/substrate ratios are at least 3 and the reaction temperature is lowered (toward 20 °C).

Registry No.—HkH, 501-30-4; HkM, 6269-25-6.

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Phase Transfer Catalysis. Preparation of Aliphatic and Aromatic Sulfonyl Fluorides

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We wish to report a very facile and convenient synthesis of organic sulfonyl fluorides employing crown ether catalysis.

Organic sulfonyl fluorides are of interest owing to their insecticidal, germicidal,[1,2] and enzyme inhibitory properties.[3-5] There are many methods available for their preparation, most of which involve halogen exchange (i.e., conversion of the corresponding sulfonyl chloride to the sulfonyl fluoride). One of the original sulfonyl fluoride preparations requires boiling the sulfonyl chloride with an aqueous solution of potassium fluoride.[6,7] This procedure results in only moderate yields (46–83%) and will not work for water-sensitive compounds. Other syntheses include (1) refluxing the corresponding sulfonyl chloride and potassium fluoride in a cosolvent system (e.g., dioxane/water) (70% yield), (2) reacting anhydrous hydrogen fluoride with the sulfonic anhydride (90–95%),[8] (3) addition of sodium nitrite to a solution of the corresponding sulfonamide in anhydrous hydrogen fluoride (53–78%),[9] and (4) heating the sulfonyl chloride with sodium fluoride suspended in tetramethylenesulfone, acetonitrile, or dimethylformamide (62–72%).[3,10]

A recently reported synthesis of sulfonyl fluorides involved conversion of the sulfonyl chloride using a dialkylaminosulfur trifluoride compound as the fluorine/chlorine exchange reagent (72–79%).[11] The reagent, however, must be prepared in two low-yield steps from a secondary amine, trimethylsilyl chloride, and sulfur tetrafluoride.[12]

In recent years, solid–liquid phase-transfer catalysis involving crown ethers has gained widespread use as a tool in organic synthesis.[13] The nucleophilic enhancement of anions by crown ethers in aprotic solvents is well known. The use of 18-crown-6 ether[14] to catalyze fluorine/halogen exchange with a wide variety of substrates has also been documented;[15] however, to the best of the authors' knowledge, no mention has been made in the literature of a crown ether catalyzed fluoride exchange reaction with organic sulfonyl chlorides.

The reaction is conducted by stirring the sulfonyl chloride and excess potassium fluoride at room temperature in acetonitrile solution or neat in the presence of 18-crown-6 ether catalyst. Representative sulfonyl fluorides have been prepared by this method in very high yield (see Table I).

$$RSO_2Cl \xrightarrow[KF,\ CH_3CN,\ RT]{\text{18-crown-6 ether}} RSO_2F + KCl$$

The reaction mixture is heterogeneous at all times, but the appearance of the solid phase changes as the reaction progresses. The reaction is exothermic, and controlled addition is sometimes necessary. The 18-crown-6 ether is catalytic (see Table I); however, the reaction will proceed in the absence of catalyst at a slower rate. All conversions are complete within 4 h and are essentially quantitative, making isolation and purification remarkably simple. Water washing easily separates the sulfonyl fluoride product from the salts. It was found that liquid sulfonyl chlorides make excellent solvents for this phase-transfer catalyzed reaction. These conversions were run neat with the potassium fluoride being phase transferred into the coreactant. For solid sulfonyl chloride reactants, acetonitrile appeared to be the solvent of choice, although other aprotic solvents may work equally well.[17]

Dansyl chloride is of importance as a fluorescent probe, but has a poor shelf life owing to its water sensitivity. This preparation allows one to prepare dansyl fluoride (**7**), which is quite stable and has the same fluorescent probe properties.[5] The

Table I. 18-Crown-6-Ether Catalyzed Conversion of Sulfonyl Chlorides to Sulfonyl Fluorides

Registry no.		Product[a]	Equiv of KF	Solvent	Mp/bp, °C	% yield[b]	Concn of crown, mol %[c]
5558-25-8	1	Methanesulfonyl fluoride	1.2		123–124	84[d]	~0.6
329-98-6	2	α-Toluenesulfonyl fluoride	2.0	CH_3CN	91–92	89	~2.0
368-43-4	3	Benzenesulfonyl fluoride	1.2		84 (8 mmHg)	92.5	~0.7
455-16-3	4	*p*-Toluenesulfonyl fluoride	2.0	CH_3CN	42.5–43.5	100	~1.0
498-83-9	5	*p*-Bromobenzenesulfonyl fluoride	2.0	CH_3CN	64–65	100	~1.0
329-20-4	6	*p*-Acetamidobenzenesulfonyl fluoride	2.0	CH_3CN	175–177	96	~1.0
34523-28-9	7	5-Dimethyl-amino-1-naphthalenesulfonyl fluoride (dansyl fluoride)	2.0	CH_3CN	48–50	100	~3.0

[a] In all cases, conversion to product was quantitative. All spectral data (IR, NMR) are consistent with the assigned structure of the isolated product. [b] Represents isolated yield. [c] In all cases, the 18-crown-6 ether was used as its acetonitrile complex. NMR analysis of the complex indicates a 2:1 ratio of acetonitrile to 18-crown-6 ether. This has been confirmed by an x-ray diffraction study.[16] [d] Yield is not optimized.

conversion can be visually monitored as the orange dansyl chloride converts to the yellow dansyl fluoride.

The mild reaction conditions, excellent yields, simple isolation and purification of products, and scalability[18] are advantages of this procedure over prior arts that require energy input, sophisticated equipment, and expensive, noncommercially available reagents.

Experimental Section

Reactions were carried out in Pyrex equipment. Sulfonyl chlorides were commercially available (Eastman Kodak Co.). Potassium fluoride was commercially available (MCB) in anhydrous form and was not dried prior to use. 18-Crown-6 ether was prepared according to a known literature procedure.[19]

Preparation of *p*-Acetamidobenzenesulfonyl Fluoride (6). Acetonitrile Method. To a mixture of *p*-acetamidobenzenesulfonyl chloride (117.0 g, 0.5 mol) and potassium fluoride (58.0 g, 1.0 mol) in 200 mL of acetonitrile was added a solution of 18-crown-6 ether/acetonitrile complex (5 g) in 100 mL of acetonitrile at room temperature (20 °C). The reaction mixture was allowed to stir overnight. It was then drowned out in 5 volumes of water. The off-white solid was collected, washed with water, and dried to provide 105.0 g of *p*-acetamidobenzenesulfonyl fluoride, mp 175–177 °C, 96% yield.

Preparation of Benzenesulfonyl Fluoride (3). Neat Method. To a solution of 18-crown-6 ether/acetonitrile complex (5 g) and benzenesulfonyl chloride (340 g, 1.93 mol) was added portionwise potassium fluoride (130 g, 2.24 mol). The reaction mixture was allowed to stir overnight after completion of the exothermic addition. One liter of water was then added, and the organic layer was separated, dried over anhydrous magnesium sulfate, and vacuum distilled to give 285.0 g of benzenesulfonyl fluoride, bp 84–85 °C (8 mmHg), 92.5% yield.

Registry No.—1 chloride derivative, 124-63-0; **2** chloride derivative, 1939-99-7; **3** chloride derivative, 98-09-9; **4** chloride derivative, 98-59-9; **5** chloride derivative, 98-58-8; **6** chloride derivative, 121-60-8; **7** chloride derivative, 605-65-2.

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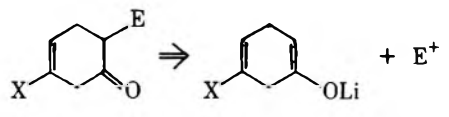
Communications

α′-Functionalization of β,γ-Unsaturated Cyclohexenones. Utilization of Silyl Enol Ethers Produced from the Lithium/Ammonia Reduction of Silyl Aryl Ethers

Summary: Lithium/ammonia reduction of isopropyldimethyl- and *tert*-butyldimethylsilyl aryl ethers provides a high-yield synthesis of 1,4-dihydroaryl silyl ethers which may be regiospecifically elaborated to nonconjugated ketones.

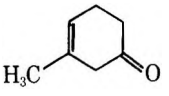
Sir: We have been faced with the need for a general method for synthesis of nonconjugated enones of the type **1a,b**. Analysis of this problem suggested that one conceptually simple solution might be via the reaction of enolate **2a,b** with an electrophilic species, E^+.



1a, X = CH_3 **2a**, X = CH_3
b, X = OCH_3 **b**, X = OCH_3

Attempts to generate enolate **2a** by addition of ketone **3** to a solution of lithium diisopropyl amide (LDA) were precluded by preferential formation of conjugated enolate **4**.[1]

Since it has been established that silyl enol ethers can be regiospecifically functionalized under kinetic conditions either directly, by electrophilic substitution reactions,[2] or via prior conversion to an enolate,[3,4] it was felt that a similar expedient with dihydroaryl silyl ethers such as **6a–c** might provide an efficient synthesis for the desired class of nonconjugated enones.



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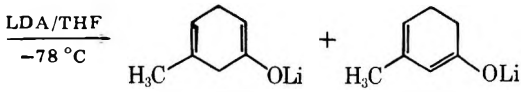
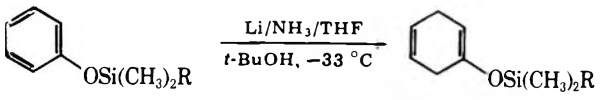


2a (~20%) **4** (~80%)

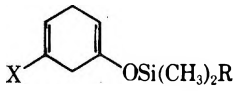
Preparation of the requisite dihydroaryl silyl ethers can be conveniently achieved by lithium/ammonia reduction of the corresponding *tert*-butyldimethylsilyl or isopropyldimethylsilyl phenyl ethers **5a–b**[5] under carefully controlled conditions[6] (see Chart I). The corresponding trimethylsilyl aryl ether **5c** is hydrolytically unstable to the reaction conditions and provides only a very poor yield of dihydroaryl isomer **6c**.



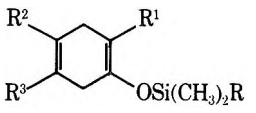
5a, R = $C(CH_3)_3$ **6a–c**
b, R = $CH(CH_3)_2$
c, R = CH_3

The dihydroaryl silyl ethers **6–15** serve as excellent substrates for further functionalization; for example, reaction of isopropyldimethylsilyl enol ether of **7b** with methyllithium[3,13] cleanly generates enolate **2a** as demonstrated by reaction with acetic anhydride (inverse addition) to produce oxygen and carbon acylated products **16**[8,9] and **17**[8,9,14] which are uncontaminated by products which would have resulted from eno-

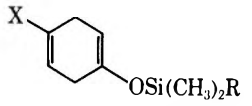
Chart I. Dihydroaryl Silyl Ethers Produced from Aryl Silyl Ethers[7-9]



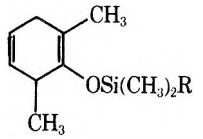
6a, X = H; R = *t*-Bu (95%)
b, X = H; R = *i*-Pr (90%)
7a, X = CH_3; R = *t*-Bu (92%)
b, X = CH_3; R = *i*-Pr (90%)
8a, X = OCH_3; R = *t*-Bu (95%)
b, X = OCH_3; R = *i*-Pr (90%)



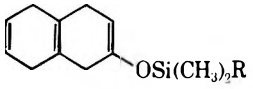
9a, R^1 = CH_3; R^2 = R^3 = H; R = *t*-Bu (96%)
b, R^1 = CH_3; R^2 = R^3 = H; R = *i*-Pr (89%)
10a, R^1 = R^2 = CH_3; R^3 = H; R = *t*-Bu (97%)
b, R^1 = R^2 = CH_3; R^3 = H; R = *i*-Pr (90%)
11a, R^1 = R^3 = CH_3; R^2 = H; R = *t*-Bu (95%)
b, R^1 = R^3 = CH_3; R^2 = H; R = *i*-Pr (93%)



12a, X = CH_3; R = *t*-Bu (95%)
b, X = CH_3; R = *i*-Pr (89%)
13a, X = OCH_3; R = *t*-Bu (85%[10])
b, X = OCH_3; R = *i*-Pr (80%[10])

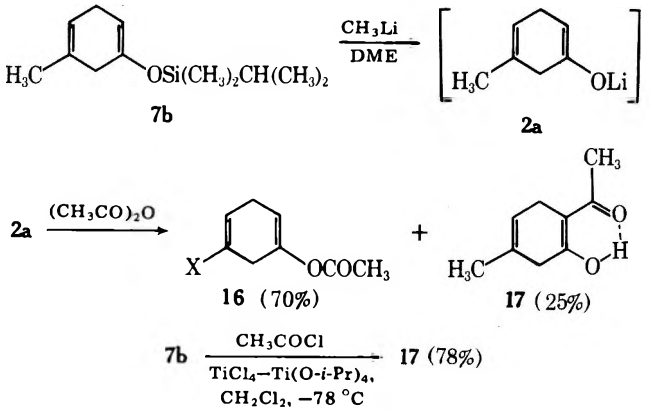


14a, R = *t*-Bu (60%[11])
b, R = *i*-Pr (54%[11])



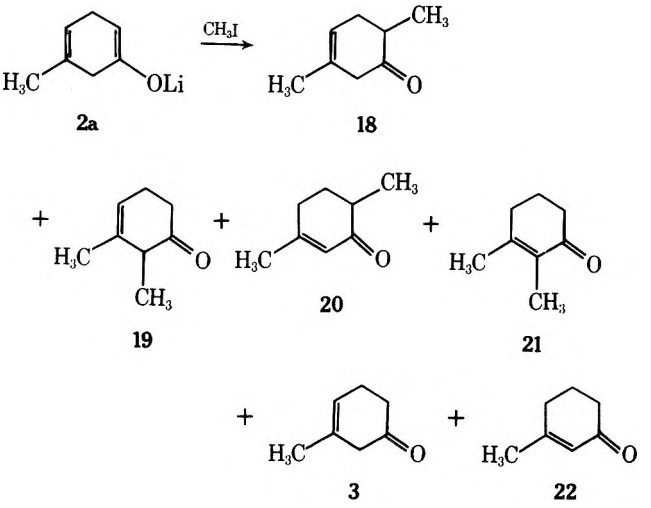
15a, R = *t*-Bu (95%[12])
b, R = *i*-Pr (91%[12])

late equilibration.[15,16] The further versatility of dihydroaryl silyl ethers is shown by the *direct* production of **17** via the $TiCl_4$ catalyzed[2] reaction of **7b** with acetyl chloride.

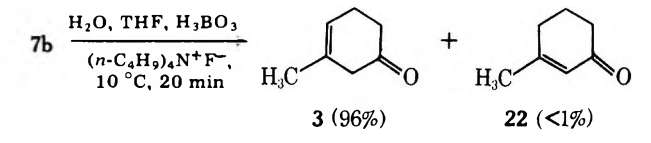


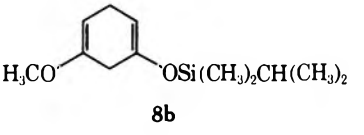
Initial attempts at alkylation of enolate **2a** were disappointing. Addition of **2a** to excess methyl iodide (with or without HMPA) does not smoothly produce the desired ketone **18**. In addition to a poor yield of **18** (25%), the mixture contains nonconjugated ketone **19** (20%), conjugated isomers **20** (5%) and **21** (5%), nonmethylated ketones **3** (10%) and **22** (5%), as well as several polyalkylated products (30%). During the course of the alkylation reaction, the initially produced alkylated ketone **18** is apparently serving as an acid to allow enolate equilibration which fosters the observed plethora of products.[17]

Dihydroaryl isopropyldimethylsilyl ethers also provide

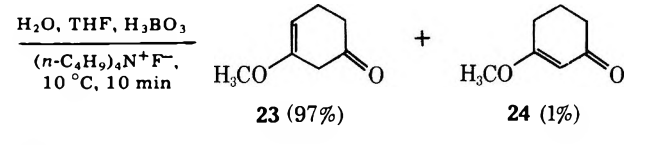


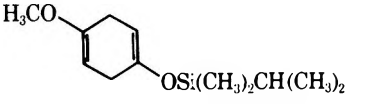
convenient substrates for the synthesis of nonconjugated ketones via tetraalkylammonium fluoride mediated hydrolysis.[18-20] Reaction of **7b** with a homogeneous solution of tetrabutylammonium fluoride[5] in aqueous tetrahydrofuran buffered with boric acid smoothly produces enone **3**. Hydrolysis of *mixed* siloxyalkoxy ethers **8b** and **13b** similarly yields the regiospecifically monoprotected diones **23** and **25**, respectively.[7-9]



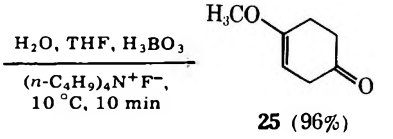


8b

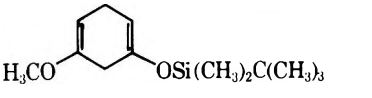




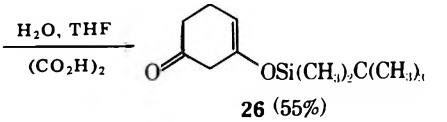
13b

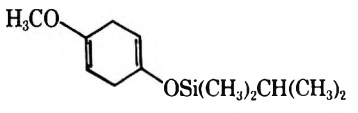


The complimentary hydrolysis of the alkyl enol ether moiety of *tert*-butyldimethyl silyl ethers **8a** and **13a** may be satisfactorily achieved under acidic conditions.[7-9,21,22]

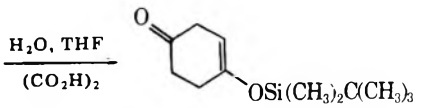


8a





13a



27 (54%)

Acknowledgment. This investigation was supported by Grant Number CA-19689-01, awarded by The National Cancer Institute, DHEW.

References and Notes

(1) This ratio was obtained by NMR analysis of the mixture of oxygen and carbon acetylated products which result from quenching the **2a/4** reaction with acetic anhydride.

(2) (a) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972); (b) K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, 1223 (1974); (c) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96,** 7503 (1974); (d) T. Mukaiyama, H. Ishihara, and K. Inomata, *Chem. Lett.*, 527 (1975); (e) *ibid.*, 531 (1975); (f) K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49,** 779 (1976); (g) M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **98,** 4679 (1976); (h) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *ibid.*, **98,** 6715 (1976).

(3) (a) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90,** 4462 (1968); (b) *ibid.*, 4464 (1968); (c) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34,** 2324 (1969); (d) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96,** 7114 (1974); (e) M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976), and references contained therein.

(4) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97,** 3257 (1975).

(5) The phenyl silyl ethers were easily prepared (average 94% yield,[7-9] 20 cases) by reaction of the appropriate phenol with either *tert*-butyldimethylchlorosilane[5a] or isopropyldimethylchlorosilane[5b] in DMF with imidazole as catalyst.[5a] (a) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94,** 6190 (1972). (b) E. J. Corey and R. K. Varma, *ibid.*, **93,** 7319 (1971).

(6) The following experiment is typical of the procedure employed for the reduction of dimethyl-*tert*-butyl and dimethylisopropylsilyl aryl ethers. A 500-mL three-necked flask is fitted with a mechanical stirrer, dry ice condenser, a Claisen adaptor to allow for the use of a septum for introducing reagents, and a stopcock for introducing ammonia gas. The system is flame dried, flushed with N_2 gas, and, after cooling, 100 mL of THF [distilled from $Na/(C_6H_5)_2CO$] and 15.0 mL of *tert*-butyl alcohol (160 mmol, distilled from sodium) are introduced via a syringe. Ammonia (250 mL, distilled from lithium) is condensed into the flask and 25 cm of lithium–1% sodium wire (0.0423 g/cm, 150 mmol) is added with cooling. After the lithium has dissolved (~10 min) the silyl aryl ether is added (25.0 mmol) and the mixture is maintained at reflux (−33 °C). After 15 min, 7.5 additional mL of *tert*-butyl alcohol (80 mmol) is added to the reaction mixture. After an additional 30 min, the excess lithium is quenched with solid anhydrous NH_4Cl. (Caution! Cooling is necessary at this point to avoid bumping.) When the blue color has been discharged, the reaction mixture is poured carefully into a vigorously stirred mixture of 750 mL of hexane/750 mL of saturated aqueous NH_4Cl. The layers are separated and the aqueous layer is extracted with 300 mL of hexane. The hexane fractions are combined, dried ($MgSO_4$), and evaporated in vacuo. The product is then vacuum distilled. Kugelrohr distillation is usually sufficient. Similarly to the corresponding reductions of alkyl phenyl ethers [W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78,** 6331 (1956); A. L. Wilds and N. A. Nelson, *ibid.*, **75,** 5360 (1953)], the reduction of 1,2,3-trisubstituted isomers **14a,b** requires more forcing conditions. This reduction can be realized by treating the substrate (25 mmol) with 50 cm of lithium–1% sodium wire (250 mmol) in 60 mL of THF/120 mL of NH_3/28 mL of *t*-BuOH (300 mmol) for 2 h at reflux (−33 °C) followed by the usual workup procedure. The dihydroaryl silyl ethers are modestly sensitive to oxidative rearomatization, especially in basic media, and are best kept cold under nitrogen for extended storage.

(7) Yields refer to isolated material of >95% purity.

(8) These compounds have spectral properties (IR, NMR, mass spectra) in accord with their assigned structures.

(9) These compounds exhibit analytical properties (exact mass and/or elemental analysis) in accord with their assigned structures.

(10) A lower boiling co-product (~10%) formed in the reductions of **13a,b** is the silyl enol ether of cyclohexanone. This product is formally derived via reductive cleavage[10a,b] of the conjugated isomer of dienes **13a,b** followed by further reduction. Control experiments suggest that **13b** is not the precursor of the observed reduction product—even with extended reaction times. (a) B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, **29,** 2102 (1964). (b) J. A. Marshall and N. H. Anderson, *ibid.*, **30,** 1292 (1965).

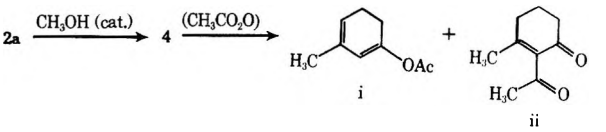
(11) Substantial (35–40%) amounts of an over-reduction product,[10] the silyl enol ether of 2,6-dimethylcyclohexanone, is also produced in this reaction, which is run under more vigorous conditions.[6]

(12) A lower boiling by-product (2–6%), 1,4,5,6,7,8-hexahydronaphthalene, is also produced in this reaction (cf. footnote 10).

(13) Cleavage of the *tert*-butyldimethylsilyl substrate **7a** with methyllithium was far more sluggish (cf. ref 3a,b).

(14) The endocyclic structure of this enol is assigned on the basis of spectral similarity with previously studied acylcyclohexanones.[14a-c] (a) E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **87,** 505 (1965). (b) S. Hunig and H. Hoch, *Justus Liebigs Ann. Chem.*, **716,** 68 (1968). (c) H. Sterk, *Monatsh. Chem.*, **100,** 1246 (1969).

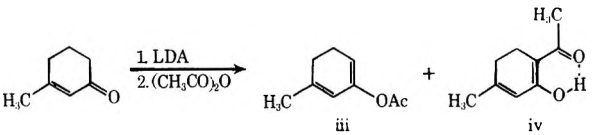
(15) Samples of oxygen and carbon acetylated compounds i[8,9] and ii[8,9] were independently prepared via acylation of enolate **4** (obtained by methanol



i ii

catalized equilibration of enolate **2a**) and were shown to be absent (<1%) from the crude **2a** acetylation reaction as judged by NMR, TLC, and VPC analyses.

(16) Samples of oxygen and carbon acetylated compounds iii[8,9] and iv[8,9,14] were independently prepared from 3-methyl-2-cyclohexen-1-one and were



iii iv

shown to be absent (<1%) from the crude **2a** acetylation reaction as judged by NMR, TLC, and VPC analysis.

(17) Alternate approaches for the direct alkylation of dihydroaryl silyl ethers are currently being evaluated.

(18) Since this reaction is run under relatively neutral conditions, it provides a useful compliment to the standard *acidic* hydrolysis of dihydroaryl alkyl ethers [cf. W. S. Jdhnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron Suppl., No. 8,* Part 2, 541 (1966)].

(19) The corresponding hydrolysis of the *tert*-butyldimethyl silyl ethers **7a, 8a,** and **13a** is less satisfactory. The longer required reaction times allow several reactions to become competitive (particularly product isomerization).

(20) Treatment of silyl enol ethers **7b, 8b,** and **13b** (2.0 mmol) with 4.0 mmol of $(n\text{-}C_4H_9)_4N^+F^-$ and 2.0 mmol of H_3BO_3 in 5.0 mL of H_2O/32 mL of THF (homogeneous solution) at 10 °C for 10 min (**7b** requires longer reaction time, 20 min) gives the corresponding ketone. The reaction mixture is then added to a vigorously stirred mixture of 200 mL of H_2O/100 mL of $CHCl_3$ at 5 °C (emulsion removed by filtration). The aqueous layer is extracted with 50 mL of $CHCl_3$. The $CHCl_3$ fractions are combined, washed with 2 × 100 mL of H_2O, dried ($MgSO_4$), and evaporated at 15 mm. The product is vacuum distilled (Kugelrohr, 0.5 mm, 40 °C). In the purification of ketone **23,** temperatures must be kept below 40 °C during evaporation and distillation to prevent double-bond isomerization.

(21) The corresponding isopropyldimethyl silyl ethers **8b,** and **13b** give lower yields owing to competitive hydrolysis of both vinyl ether moieties.

(22) **8a** (5.0 mmol) is treated with a homogeneous solution of $(HO_2C)_2 \cdot 2H_2O$ (65 mmol, 8.2 g) in 20 mL of THF at 30 °C for exactly 10 min (cleavage of 13a requires 7 min). The reaction mixture is quickly added to 200 mL of hexane/200 mL of 5% Na_2CO_3. (Caution! Foaming may occur.) The aqueous layer is extracted with 100 mL of hexane. The hexane fractions are combined, dried ($MgSO_4$), and evaporated in vacuo. The product is kept under vacuum (0.5 mm) for 4 h to remove *tert*-butyldimethylsiianol and is then distilled.

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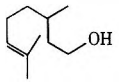
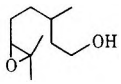
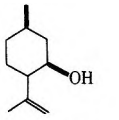
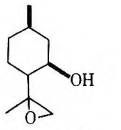
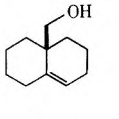
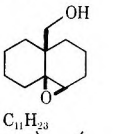
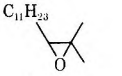
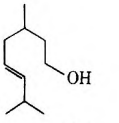
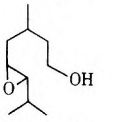
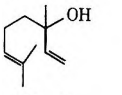
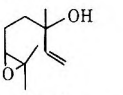
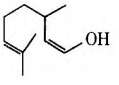
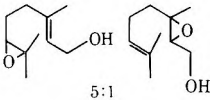
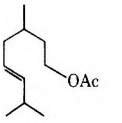
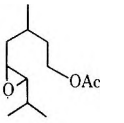
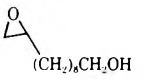
Organoselenium Chemistry. Epoxidation of Olefins with Benzeneseleninic Acid and Hydrogen Peroxide ("Benzeneperoxyseleninic Acid")

Summary: Benzeneseleninic acid and hydrogen peroxide generate in situ "benzeneperoxyseleninic acid" which functions as an epoxidizing agent.

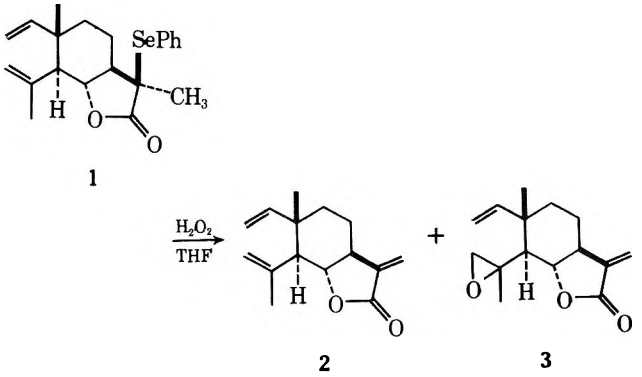
Sir: We have observed the formation of epoxides during the oxidation (50% aqueous hydrogen peroxide) and subsequent elimination of phenylseleno groups adjacent to carbonyls.[1]

Table I. Epoxidation of Olefins with Benzeneperoxyseleninic Acid[a]

Starting olefin	Product	Solvent	PhSeOOH, equiv	Hydrogen peroxide, equiv	Reaction[b] time, min	% yield[c] of epoxide, % recovered starting material
		MeOH	1.2	1.2	20	75
		THF	1.2	1.2	20	85
		MeOH	1.2	1.2	20	71
		THF	1.0	1.0	20	81
		MeOH	1.2	1.8	20	75
$CH_3(CH_2)_{10}CH{=}C(CH_3)_2$		THF/MeOH/EtOH	1.2	1.4	45	85
		MeOH	1.2	1.4	20	47 (42)
		MeOH	1.2	1.4	30	63 (8)
	 5:1	MeOH	1.2	1.4	30	65
		MeOH	1.2	1.4	30	58 (26)
$CH_2{=}CH(CH_2)_8CH_2OH$		MeOH	1.2	1.4	20	35 (48)

[a] All reactions were carried out at pH 7 in phosphate buffered solution. [b] After the indicated time the reaction mixture was treated with silica gel for ~60 min. [c] All compounds were fully characterized by spectral methods. Yields reported are for isolated, chromatographically pure substances.

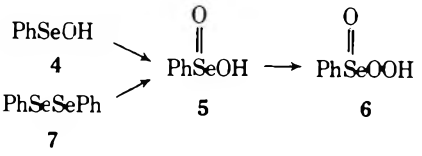
During the elimination of benzeneselenenic acid from the selenoxide derived from treatment of selenide **1** with 8.0 equiv of 50% hydrogen peroxide there was obtained in addition to dehydrosaussurea lactone **2** (18%) a 30% yield of epoxide **3**.[2]



1 **2** **3**

On the basis of previous work[3] we had anticipated the smooth conversion of selenide **1** to dehydrosaussurea lactone (**2**) in high yield. When exactly 2.0 equiv of hydrogen peroxide was employed, no epoxide formation could be detected and a 93% yield of dehydrosaussurea lactone was realized.

It has previously been established that benzeneselenenic acid (**4**) produced during the elimination of a selenoxide reacts further with hydrogen peroxide to generate benzeneseleninic acid (**5**) (eq 1).[4] We now suggest on the basis of the preliminary



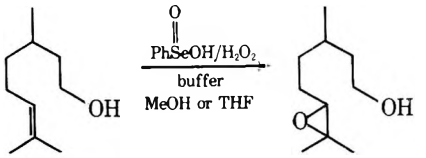
(1)

4 **5** **6** **7**

results above that benzeneseleninic acid in the presence of hydrogen peroxide generates in situ benzeneperoxyseleninic acid (**6**) which functions as an epoxidizing agent (vide infra).[5] To our knowledge no prior report on the generation and epoxidizing ability of benzeneperoxyseleninic acid has appeared in the literature.[6,7] Benzeneseleninic acid is commonly prepared by the treatment of diphenyl diselenide (**7**) with hydrogen peroxide.[8]

We now report that olefins undergo smooth epoxidation in either methanol or tetrahydrofuran using benzeneperoxyseleninic acid readily generated in situ from benzeneseleninic acid and 50% hydrogen peroxide (Table I).[9] The reactions are best carried out in buffered (pH 7, phosphate) solution to avoid diol formation.[10] We have also observed that the rate of the reaction and yield are highly dependent upon the nature of the workup. For example, treatment of citronellol (**8**) with 1.0 equiv of benzeneseleninic acid and 2.0 equiv of 50% hy-

drogen peroxide in tetrahydrofuran buffered at pH 7 revealed on TLC analysis after ~20 min the complete conversion of starting olefin to the desired epoxide **9**. NMR analysis of the



8 **9**

crude product after workup revealed that >90% of the starting olefin remained. If, however, after initial mixing of reagents (~20 min) one pours the reaction contents onto a silica gel plate (for convenience) and elutes after ~60 min, an 85% yield of pure epoxide **9** can be realized. In buffered methanol solution using 1.2 equiv of benzeneseleninic acid and 1.2 equiv of 50% hydrogen peroxide citronellol gave, using the same silica gel treatment, a 75% isolated yield of pure epoxide.

The stereoselectivity observed in the epoxidation of olefinic alcohols with benzeneperoxyseleninic acid complements that observed in the transition metal catalyzed epoxidations of olefinic alcohols by *tert*-butyl hydroperoxide.[11] Geraniol and linalool are selectively oxidized in the presence of vanadium or molybdenum catalysts by alkyl hydroperoxides to 2,3-epoxygeraniol and 1,2-epoxylinalool, respectively. In contrast, linalool and geraniol were epoxidized with benzeneperoxyseleninic acid predominantly at the olefin furthest removed from the hydroxyl group (see Table I).[12]

The following experimental procedure indicates the simplicity of the method. A solution of benzeneseleninic acid (454 mg, 2.4 mmol) in 4 mL of methanol was treated with 160 μL (2.4 mmol) of 50% hydrogen peroxide. After ~5 min, 1.5 mL of phosphate buffer (pH 7) was added followed by the addition of citronellol (312 mg, 2.0 mmol) in 2 mL of methanol. The reaction was quenched after 20 min with 20 g of silica gel. After 60 min the silica gel was washed with a 1:1 mixture of ether and hexane leaving 302 mg of crude product. Purification on 15 g of silica gel gave 264 mg (75%) of pure epoxide (**9**) as a colorless liquid.

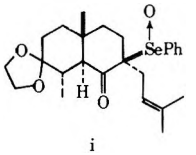
In summary, benzeneperoxyseleninic acid represents a new reagent for the facile, rapid, high yield conversion of substituted olefins into epoxides. The syn-directive effect observed in both the peracid and the transition metal/hydroperoxide epoxidation of allylic alcohols does not appear to play a major role in epoxidation with benzeneperoxyseleninic acid.

Acknowledgment. We thank the National Institutes of Health (CA 13689-05), Glidden Organics, and Shell Development Co. for support of this research. We thank Mr. George Majetich for providing us with a sample of 10-hydroxymethyl-$\Delta^{1,9}$-octalin.

References and Notes

(1) For the use of α-phenylseleno carbonyl compounds as precursors to α,β-unsaturated ketones and esters, see H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973).

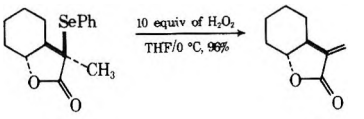
(2) During the elimination of benzeneselenenic acid from selenoxide i in the



i

presence of excess hydrogen peroxide we have observed epoxidation of the prenyl double bond.

(3) We have previously demonstrated [P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974)] that α-methyl-α-phenylselenolactones undergo



ii iii

oxidation with excess hydrogen peroxide providing after elimination of benzeneselenenic acid near-quantitative yields of α-methylene lactones (cf. ii → iii).

(4) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

(5) $PhSeO_3H$ has been proposed as the active reagent in hydrogen peroxide oxidations of divalent selenium compounds.[6b]

(6) (a) K. B. Sharpless and K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975); (c) D. L. Klayman and W. H. H. Gunther, "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973.

(7) Hydrogen peroxide in the presence of selenium dioxide has been reported to hydroxylate olefins [N. Sonoda and S. Tsutsumi, *Bull. Soc. Chem. Jpn.*, **38**, 958 (1965)].

(8) J. D. McCullough and E. S. Gould, *J. Am. Chem. Soc.*, **71**, 674 (1949).

(9) Use of diphenyl diselenide in place of benzeneseleninic acid during epoxidation of citronellol in tetrahydrofuran with excess hydrogen peroxide gave a 69% yield of epoxide **9**.

(10) The epoxidation reaction appears to be catalytic with respect to benzeneseleninic acid; however, the reaction requires very long reaction times during which diol formation predominates.

(11) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

(12) Epoxidation of geraniol and linalool with standard peracids (e.g., *m*-chloroperbenzoic acid) results in poor selectivity.

(13) Fellow of the Alfred P. Sloan Foundation.

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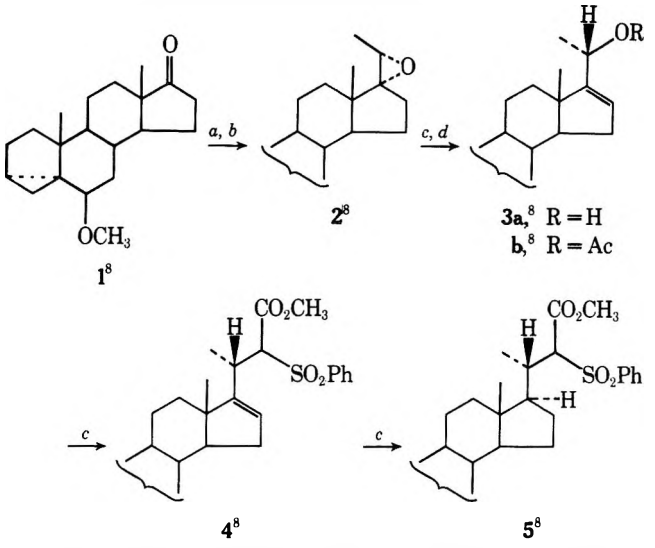
Stereocontrolled Synthesis of the Ecdysone Side Chain via Organopalladium Chemistry

Summary: Two stereocontrolled syntheses of (22*R*)-25-dihydroxycholesterol and one of the 22*S* isomer from 6β-methoxy-3,5-cycloandrostan-17-one are reported.

Sir: The ability to introduce a cholesterol-type side chain with stereochemical control continues as a major challenge that has been heightened by the importance of natural products containing modified side chains.[1-5] Most noteworthy are the hydroxylated side chains that appear in the ecdysones[2,3] and the metabolites of vitamin D.[4,5] We wish to report the stereocontrolled synthesis of (22*R*)-25- and (22*S*)-25-dihydroxycholesterol which, by known procedures,[3] could be converted into the insect molting hormones. This approach demonstrates the use of the palladium-based alkylations for control of acyclic stereochemistry,[6] the versatility of the α-sulfonyl esters, and the introduction of a vinyl group at an allylic carbon with control of stereochemistry at that carbon.

The key intermediate is the sulfone ester 4 available from 6β-methoxy-3,5-cycloandrostan-17-one (1),[7,8] mp 65–66 °C, as outlined in Scheme I. Condensations with ethylidenetriphenylphosphorane followed by epoxidation gave **2**,[8] mp 97–98 °C. Treatment with 10 equiv of lithium diisopropylamide in 4:1 hexane–DME initially at −78 °C and subsequently warming to room temperature gave in 77% isolated yield the desired allylic alcohol **3a**, oil, $[\alpha]^{25}_D$ +38.4° ($CHCl_3$, c 0.742).[9] Addition of a solution of methyl phenylsulfonylsodioacetate in THF to a solution of **3b**[8] and 9 mol % tetrakis(triphenylphosphine)palladium in THF at room temperature and subsequent reflux led to an 85% yield of **4**,[8] mp 166–167

Scheme I. Preparation of Sulfone Ester 5



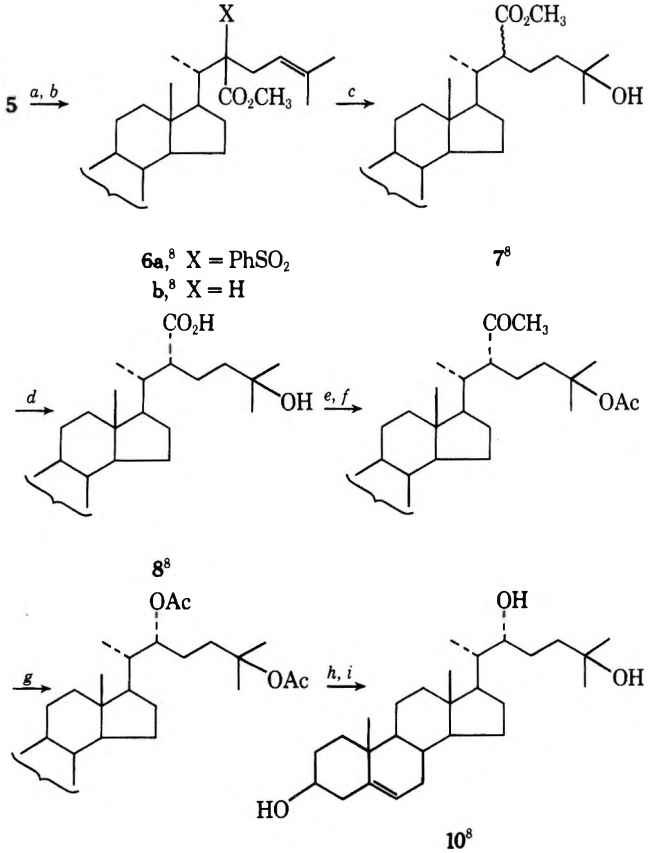
1[8] 2[8] 3a,[8] R = H; b,[8] R = Ac 4[8] 5[8]

[a] $Ph_3P^+CH_2CH_3$, Br^-, KOC_4H_9-*t*, THF, reflux, 76%. [b] MCPBA, $CHCl_3$, −10 °C, 74%. [c] See text. [d] Ac_2O, pyridine, room temperature, 97%.

°C, presumably as a diasteromeric mixture at C(22) but a single stereochemistry at C(20) (vide infra). Hydrogenation over 5% Pd–$BaCO_3$ gave **5**,[8] mp 180–183 °C, quantitatively.

In the first conversion of **5** to the desired dihydroxy compound (see Scheme II), alkylation to **6a**[8] gave an isomeric

Scheme II. Preparation of (22*R*)-25-Dihydroxycholesterol

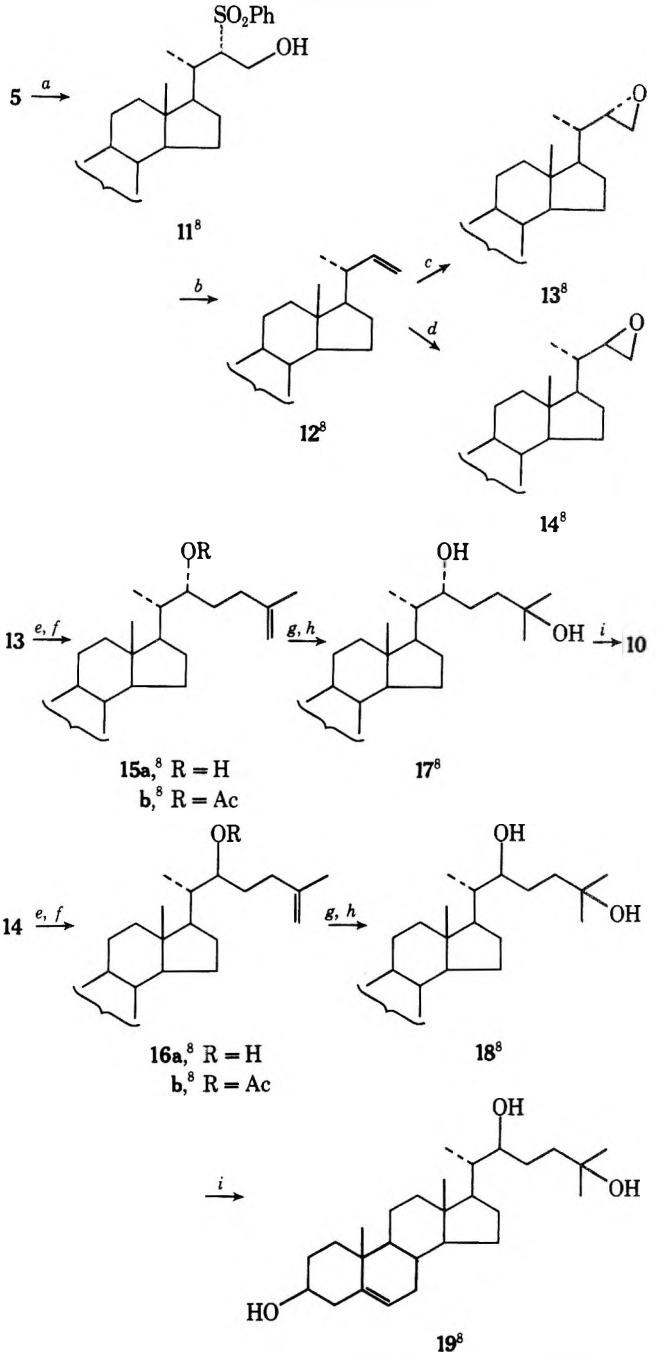


6a,[8] X = $PhSO_2$; b,[8] X = H 7[8] 8[8] 10[8]

[a] NaH, PhH, DMF, γ,γ-dimethylallyl bromide, room temperature, 80%. [b] 6% Na(Hg), CH_3OH, Na_2HPO_4, −10 °C. [c] $Hg(OAc)_2$, THF, CH_3CN, H_2O, room temperature, 71%. [d] NaOH, CH_3OH, reflux, 96%. [e] CH_3Li, ether, −10 °C, 53%. [f] 4-$(CH_3)_2NC_5H_4N$, Ac_2O, $CHCl_3$, room temperature, 66%. [g] MCPBA, $CHCl_3$, $NaHCO_3$, room temperature, 34%. [h] $LiAlH_4$, ether, room temperature, 93%. [i] TsOH, H_2O, DME, reflux, 81%.

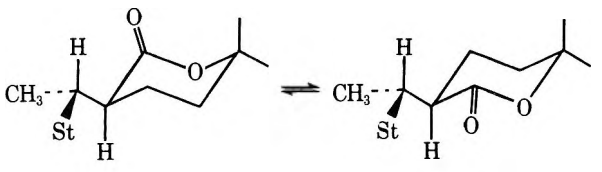
mixture at C(22) which could be separated.[10] However, separation of isomers is unnecessary and undesired. Hydration of the double bond introduced the 25-hydroxyl group (i.e., **7**). The key step in this sequence is the base-catalyzed hydrolysis of the hydroxy ester [isomeric at C(22)] which leads to a single hydroxy acid **8**.[8] Assignment as **8** was established by reesterification with diazomethane back to one epimer of **7**.[8] Each epimer of **7** had, in turn, been correlated with the known (22*R*)- and (22*S*)-hydroxycholesterols. Thus, the configuration at C(22) is *R* and that at C(20) is confirmed as *S* as depicted. That epimerization at C(22) involved participation of the hydroxy group at C(25) via the lactones **9a** and **9b** was

Scheme III. Preparation of (22*R*)-25- and (22*S*)-25-Dihydroxycholesterol



11[8] 12[8] 13[8] 14[8] 15a,[8] R = H; b,[8] R = Ac 16a,[8] R = H; b,[8] R = Ac 17[8] 18[8] 19[8]

[a] $LiAlH_4$, ether, room temperature, 94%. [b] 6% Na(Hg), CH_3OH, room temperature, 77%. [c] I_2, AgOAc, CH_2Cl_2, $NaHCO_3$, −10 °C, then CH_3OH, K_2CO_3, reflux, 83%. [d] MCPBA, $CHCl_3$, $NaHCO_3$, −20 °C, 79%. [e] See text. [f] Ac_2O, C_5H_5N, reflux, 93–100%. [g] See *d*, 65–66%. [h] See *a*, 87–98%. [i] TsOH, DME, H_2O, reflux, 81–96%.



9a 9b

St = steroid nucleus

supported by the complete absence of epimerization upon hydrolysis of the epimerially pure unsaturated esters **6b**. Since the *A* value of an ethyl group (1.75) is larger than that for a carboalkoxy group (~1–1.2),[11] **8b** would be expected to be the more stable isomer as observed. Conversion of the carboxy group to an hydroxy group employed the Baeyer–Villiger procedure and allowed obtention of the pure (22*R*)-25-dihydroxycholesterol,[8] mp 253–255 °C, which, owing to its insolubility, was further characterized as its 3,22-diacetate,[8] mp 150 °C, $[\alpha]^{25}_D$ −25.5° ($CHCl_3$, c 0.51).

Scheme III outlines a synthesis of both the 22*R* and 22*S* isomers and demonstrates the use of the sulfone ester in synthesis. Conversion of this group to a terminal vinyl group [**12**,[8] mp 39–40 °C, $[\alpha]^{25}_D$ +36.2° ($CHCl_3$, c 1.190)] proceeded smoothly via the hydroxy sulfone **11**[8] (mp 98–103 °C) by direct reductive elimination.[12] Formation of the epoxide via the iodohydrin[13] gave **13**[8] (mp 90–91 °C) contaminated by a small amount of **14**, whereas, direct epoxidation with MCPBA gave predominantly **14**,[8] mp 119–120 °C.[14] Coupling of each epoxide with methallylmagnesium chloride in THF at room temperature (93%), acetylation, epoxidation, and reduction completed the synthesis of each epimerically pure 6β-methoxy-22,25-dihydroxy-3,5-cyclocholesterol. **17**[8]: foam; $[\alpha]^{25}_D$ +46.4° ($CHCl_3$, c 0.86); NMR δ 1.32 (s, 6 H), 1.05 (s, 3 H), 0.96 (d, *J* = 7 Hz, 3 H), 0.77 (s, 3 H). **18**:[8] mp 111–113 °C; $[\alpha]^{25}_D$ +30.3° ($CHCl_3$, c 0.93); NMR δ 1.25 (s, 6 H), 1.04 (s, 3 H), 0.92 (d, *J* = 7 Hz, 3 H), 0.74 (s, 3 H). Solvolytic cyclopropyl ring opening of **17** produced (22*R*)-25-dihydroxycholesterol (**10**) identical with the previously prepared sample. Identical treatment of **18** produced the corresponding 22*S* isomer **19**,[8] mp 186–187 °C, $[\alpha]^{25}_D$ −34.4° (methanol, c 0.72).

Since the cholesterol nucleus has been converted to the ecdysone nucleus,[3] these intermediates can serve as precursors to the commercially important ecdysones. Furthermore, the nature of the side-chain substitution provides great flexibility for the synthesis of many other important side-chain modified steroids. More generally, this strategy can be envisioned as an approach to attach an acylic side chain in a stereocontrolled fashion onto a ring system.

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(8) Spectroscopic data and elemental composition in full accord with the assigned structure have been obtained.

(9) 6β-Methoxy-17α-hydroxy-17β vinyl-3,5-cycloandrostane is obtained as a by-product whose amount varies with the choice of lithium dialkylamide.

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(14) Confirmation of the stereochemical assignment was obtained by hydrogenation of **15a** and **16a**, respectively, and subsequent solvolytic opening of the cyclopropyl ether to (22*R*)- and (22*S*)-hydroxycholesterol. See ref 9.

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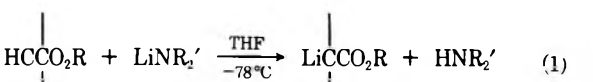
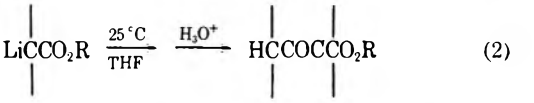
The Self-Condensation Reaction of Lithium Ester Enolates. Isolation of a Ketene Intermediate

Summary: Warming a tetrahydrofuran solution of lithio *tert*-butyl bis(trimethylsilyl)acetate to 25 °C produces bis(trimethylsilyl)ketene.

Sir: Solutions of ester enolates prepared by addition of esters to lithium amide bases in tetrahydrofuran (THF) are stable indefinitely at −78 °C[1] (eq 1). However, such solutions normally turn yellow upon warming to room temperature and quenching produces β-keto esters (eq 2).[2] This inherent po-



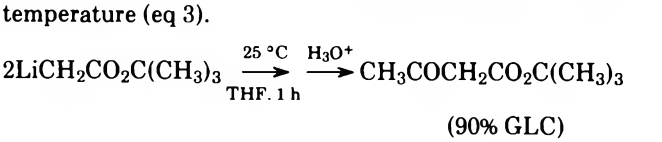
(1)



(2)

tential for self-condensation represents a major difference between ester enolates and ketone or aldehyde enolates and is perhaps a primary reason for the relatively late development of the chemistry of the aliphatic ester enolates.

A simple mechanism for the formation of condensation products is reversal of eq 1 to give small amounts of starting ester which then condenses with ester enolate. However, solutions of lithio *tert*-butyl acetate, which are prepared free of amine,[2a] nevertheless form condensation products at room temperature (eq 3).



(90% GLC)

(3)

Similar condensations have been observed with zinc ester enolates (Reformatsky reagents).[3] Vaughan suggested a ketene intermediate for the self-condensation of the reagent prepared from ethyl α-bromoisobutyrate and zinc metal as shown in eq 4.[4]

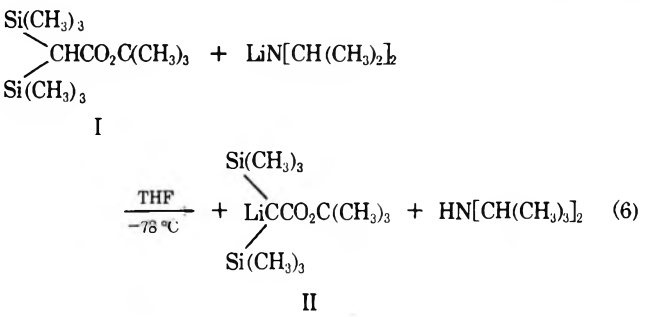
$$BrZnC(CH_3)_2CO_2C_2H_5 \rightarrow (CH_3)_2C{=}C{=}O + BrZnOC_2H_5 \quad (4)$$

$$(CH_3)_2C{=}C{=}O + BrZnC(CH_3)_2CO_2C_2H_5 \xrightarrow{H_3O^+} (CH_3)_2CHCOC(CH_3)_2CO_2C_2H_5 \quad (5)$$

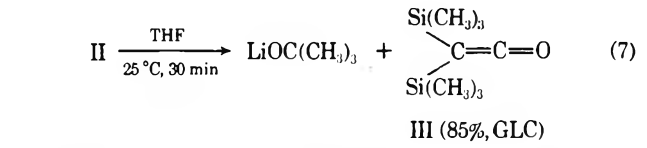
Ketene intermediates have also been proposed for the E_1CB mechanism of hydrolysis of malonic and β-keto esters.[5,6]

We report here what is to our knowledge the first isolation of a ketene from the decomposition of an ester enolate.

Addition of *tert*-butyl bis(trimethylsilyl)acetate, I, to an equivalent amount of lithium diisopropylamide gave the corresponding ester enolate, II (eq 6).[7] Warming solutions of



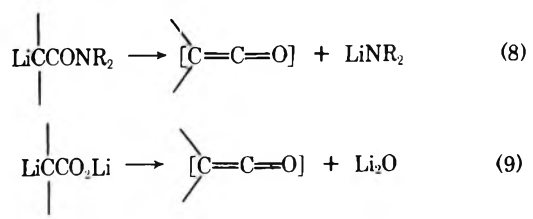
I II to room temperature did not produce the usual yellow color indicative of ester condensation. Instead, the solution remained colorless and GLC analysis showed the presence of a single product, identified as bis(trimethylsilyl)ketene, III (eq 7). Vacuum distillation of the reaction mixture gave pure samples of III [60%, bp 20 °C (2 mm)].



III (85%, GLC)

Bis(trimethylsilyl)ketene has previously been obtained as a side product of a Grignard synthesis of trimethylsilyl butoxyacetylene.[8] The present assignment of structure rests on a comparison of IR bands [2085, 1295 cm^{-1} (lit.[8] 2085, 1295 cm^{-1})], the ^1H NMR spectrum (CCl_4) δ 0.25(s), and ethanolysis with acidic ethanol to give ethyl bis(trimethylsilyl)acetate.[9]

The ability to isolate ketene rather than condensation product in the present case is clearly due to the steric hindrance to further reaction presented by the bulky trimethylsilyl groupings in III.[10] We are now attempting to obtain evidence for the formation of ketene intermediates in the self-condensation of simple aliphatic lithium ester enolates. We note that a ketene mechanism provides a simple explanation for the much greater stability (compared to lithium ester enolates) reported for the enolates of *N,N*-dialkylamides[11] and lithium carboxylates,[12] both of which have exceptionally poor leaving groups (eq 8, 9).



Acknowledgment is made to the National Science Foundation for partial support of this research.

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(10) For example, III appears to be inert to the methyl Grignard reagent and reacts only sluggishly with *n*-butyllithium at 25 °C.
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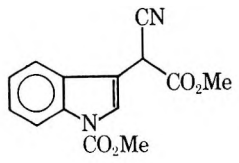
Oxazoles in Organic Chemistry. Synthesis of the Antitumor Agent Ellipticine

Summary: An efficient total synthesis of the alkaloid ellipticine through the intermediacy of a substituted oxazole has been achieved. The versatility of this intermediate for the preparation of peripherally modified analogues is emphasized.

Sir: The chemistry of oxazoles was first seriously investigated when the antibiotic penicillin was believed to contain this heterocyclic moiety.[1] More recently, the Diels–Alder reaction of substituted oxazoles has been found to provide a convenient method for the preparation of pyridoxine (vitamin B_6) and its analogues and homologues.[2] The azadiene component of the oxazole generally condenses with a dienophile in a highly regiospecific fashion to furnish a substituted pyridine base of the isonicotinic acid series (the electron-withdrawing group of the dienophile assumes position 4 of the pyridine ring[3]).

Our interest in the development of a general strategy for the preparation of several therapeutically important alkaloids led us to further pursue the chemistry of this class of heterocycles. Ellipticine (**6**), an alkaloid present in plants of genera *Ochrosia* and *Aspidosperma*, has stimulated numerous synthetic efforts because of its potent antitumor activity.[4] We chose this molecule as the first simple target in our pursuit of a general oxazole based strategy for alkaloid synthesis.

The key intermediate in our planned scheme, the 5-substituted oxazole **4**, was synthesized starting from gramine. Thus, following a general method for the preparation of indolyl aliphatic acids reported by Suvorov,[5] indoleacetonitrile (from gramine, KCN, CH_3I)[6] was dicarbomethoxylated (dimethyl carbonate, NaOMe, benzene) to give **1**. Further treatment with NaOMe/CH_3I proceeded with loss of the *N*-carbomethoxy group and C-methylation to yield the re-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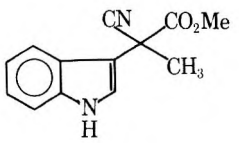
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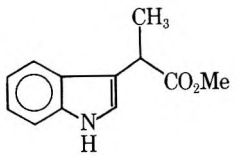
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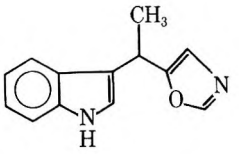
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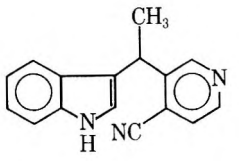
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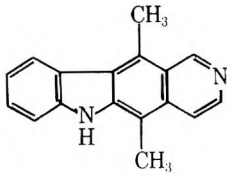
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ported product **2**, which on hydrolysis, decarboxylation, and esterification provided methyl 2-(3-indolyl)propionate (**3**) in 74% yield (KOH–ethylene glycol at 195 °C, 13 h, then refluxing methanol with acid-washed AG 50W-X2 as catalyst, 6 h).[7] Reaction of this ester with excess α-lithiated methyl isocyanide ($LiCH_2N{\equiv}C$, 4 equiv, −50 °C) followed by warming to 0 °C and quenching with acetic acid provided the crystalline oxazole **4** (80% yield after silica gel chromatography, mp 74–75 °C).[8] Diels–Alder reaction of **4** with excess acrylonitrile in acetic acid at 145 °C for 24 h gave 3-[1-(indol-3-yl)ethyl]pyridine-4-carbonitrile (**5**) in 16% yield after two successive chromatographic purifications: NMR ($CDCl_3$) δ 8.66 (d, 1 H, J = 2 Hz), 8.56 (d, 1 H, J = 6 Hz), 8.25 (br s, 1 H), 7.48–6.96 (m, 6 H), 4.74 (q, 1, J , 9 Hz), 1.79 (d, 3 H, J = 9 Hz).

The synthesis of ellipticine is formally completed at the stage for the same pyridinecarbonitrile **5** was recently prepared by Sainsburg and Schinazi by another route and converted in two additional steps to the target molecule.[9] Thus, following their procedure, addition of methyllithium to **5** (4 equiv) followed by hydrolysis and cyclization with 20% acetic acid gave a yellow solid in 80% yield whose spectral and physical properties were in accord with those reported for ellipticine.[9]

Although the yield in the Diels–Alder reaction is somewhat low,[10] the simplicity of the overall scheme makes our synthesis competitive with existing methods. In addition, since analog studies have revealed that skeletal modifications of ellipticine diminish its antitumor activity, the generation of chemical variants has focused on peripheral modifications of the parent molecule.[11] The oxazole based strategy should permit easy access to analogues containing peripherally modified D rings, for either the α-metallated isonitrile used to generate the oxazole or the dienophilic component employed in the Diels–Alder reaction is readily varied.

Such modifications will be the subject of a future communication. The application of oxazoles to the synthesis of benzylisoquinolines and benzazepines has also been accomplished, and will be reported separately.[12]

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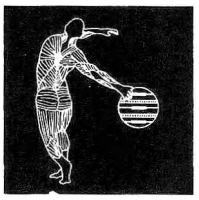

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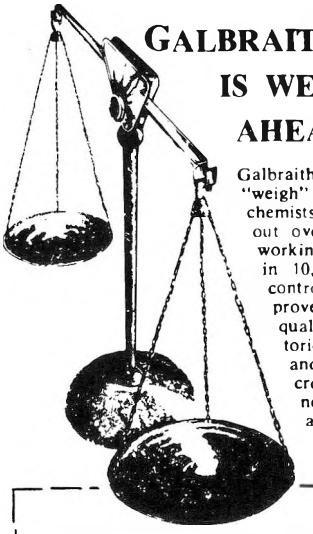

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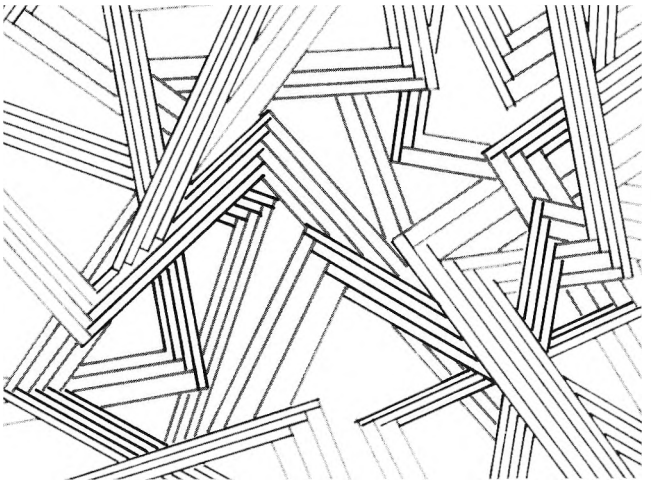

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Oxygen and Nitrogen Crowns

Macrocyclic complexing agents

Crown ethers[1] are a class of macrocyclic polyethers, the earliest of which, **dibenzo-18-crown-6**, was synthesized by C.J. Pedersen in 1967.[2] The synthetic utility of crown ethers arises from their ability to solvate cations of alkali, alkaline earth and transition metal salts. They thus increase the solubility of ion pairs, providing highly reactive unsolvated anions in nonpolar, aprotic solvents. These unsolvated ("naked")[3] anions show enhanced reactivity as nucleophiles, bases and oxidants, facilitating reactions under much milder conditions than are possible in conventional hydrolytic media. The following examples outline the remarkable synthetic utility of crown ethers.

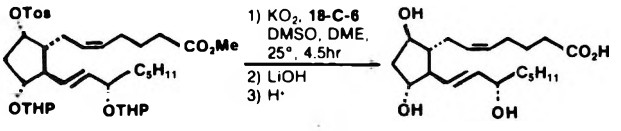
Sterically hindered esters of 2,4,6-trimethylbenzoic acid, which are resistant to hydrolysis by aqueous KOH, are readily saponified by the **dicyclohexyl-18-crown-6** complex of KOH in refluxing aromatic solvents.[4]

It has also been reported that the **dicyclohexyl-18-crown-6** complexes of potassium bromide and potassium iodide in acetone at room temperature convert *n*-butyl brosylate to the corresponding halide in clean, second-order reactions.[5]

$$[K\,Dicy\text{-}18\text{-}C\text{-}6]^+X^- + n\text{-}BuOBs \xrightarrow[25°]{\text{acetone}} [K\,Dicy\text{-}18\text{-}C\text{-}6]^+OBs^- + n\text{-}BuX$$

X = Br, I

E.J. Corey and co-workers[6] reported that **18-crown-6** facilitates the dissolution of potassium superoxide in solvents such as DMSO, DMF, DME and ether. This highly reactive superoxide acts as an effective nucleophile, replacing good leaving groups such as mesylate, tosylate and bromide by hydroxyl in high yields. This technique has been applied to the epimerization of a prostaglandin.[6]



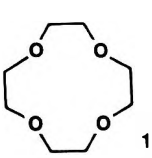
The carboxylate ion is quite nucleophilic in nonpolar solvents when used with crown ethers, and can be used to synthesize phenacyl esters, anhydrides and lactones which are difficult to obtain by classical procedures.[7] Phenacyl esters have found utility in trace fatty acid analysis.[8]

$$RCO_2K \xrightarrow[18\text{-}C\text{-}6]{BrCH_2COPh} RCO_2CH_2COPh$$

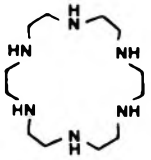
The presence of crown ethers has also enabled the use of mild bases in the Wittig reaction. As a result, a remarkable effect of solvent (CH_2Cl_2 *vs.* THF) on the stereochemistry of the products is observed.[9]

$$PhCHO + [Ph_3\overset{+}{P}CH_2R]\,Br^- \xrightarrow[K_2CO_3,\ CH_2Cl_2]{18\text{-}C\text{-}6} Ph\text{-}CH{=}CHR$$

Aldrich is pleased to introduce **12-crown-4** and **hexacyclen** to its existing line of crown ethers.



12-Crown-4



Hexacyclen

12-Crown-4 has been shown to solubilize $KMnO_4$ in benzene, and this reagent has been used to oxidize olefins to acids and active methylenes to carbonyl functions in quantitative yields.[10]

$$PhCH{=}CHPh \xrightarrow[KMnO_4]{12\text{-}C\text{-}4,\ PhH} 2\ PhCOOH \qquad 100\%$$

$$PhCH_2Ph \xrightarrow[KMnO_4]{12\text{-}C\text{-}4,\ PhH} PhCOPh \qquad 100\%$$

The role of lithium ion in lithium organocuprate complexes is better understood as a result of reactivity studies performed in the presence of **12-crown-4**. Lithium ion solvated by **12-crown-4** was found to *inhibit* the reactivity of lithium organocuprates in reactions involving enones, acid chlorides and β-keto esters.[11]

Hexacyclen is the nitrogen analog of **18-crown-6** in which the secondary amines act as excellent electron donors to transition metal cations exhibiting Lewis acidity.[12] The macrocyclic polyamines related to **hexacyclen** form complexes with transition metals which are less stable to acids than are regular amine-metal complexes. These metal-polyamine complexes have found utility as thermally activated curing agents for epoxy resins.[13]

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