/ VOLUME 41 MARCH 5, 1976 NUMBER 5 JOCEAH

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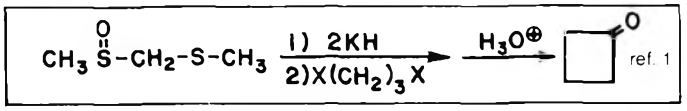
VOLUME 41, NUMBER 5 MARCH 5, 1976

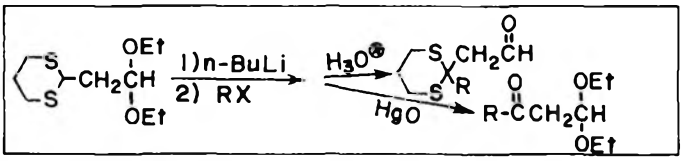
MAKING IT WITH SULFUR

Sulfur activated methylenes undergo typical reactions of other activated methylenes (Aldol, Alkylation, Mannich, Thorpe, Claisen, etc.) In addition they impart unique qualities to the molecules they inhabit, making them some of the most versatile of all synthetic intermediates

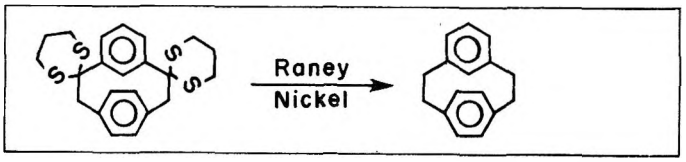
I. **Bis Sulfur Activated Methylenes:** Bis sulfur activated methylenes form stable carbanions, can be alkylated, and can be hydrolized to carbonyls. They are the equivalents of ACYL ANIONS. Typical of this group are **Methyl methylsulfinylmethyl sulfide (MMSMS)** and **m-Dithiane.** They are readily aklylated or diakylated, yielding aldehydes or ketones.



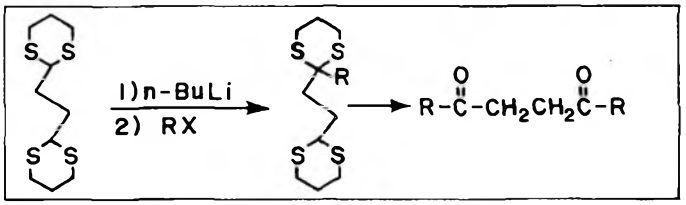
MMSMS may also be used to prepare esters[2], phenylacetic acids[3], and amino acids.[4] **m-Dithiane** may be used to prepare α-diketones, β-ketoaldehydes, α-ketoacids, and 2-hydroxy-1,3-diketones[5]. **m-Dithiane** offers the additional advantage that it is stable to aqueous acid allowing the selective protection of one carbonyl in a dicarbonyl system.



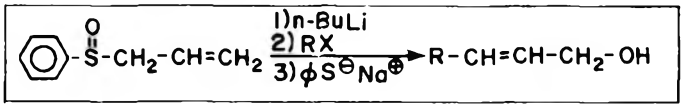
Alkylated dithianes may also be converted to hydrocarbons by Raney nickel desulfurization.



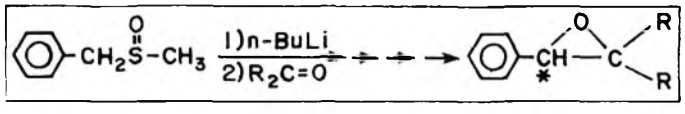
2-Aryl-m-dithianes are prepared from the reaction of the appropriate aldehyde with **1, 3-Propanedithiol[6],** and are useful for the preparation of aryl ketones and cyclophanes. It has recently been shown that **2, 2'-Ethylene bis (m-dithiane)** is readily monoaklylated and that it may subsequently be further alkylated to yield γ-diketones[7].



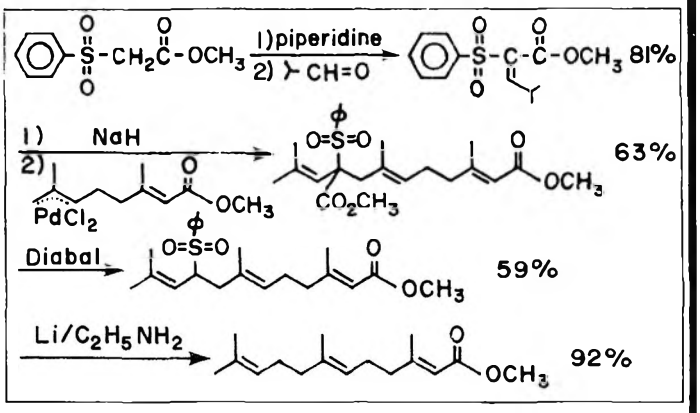
II. **Preparation of Allylic Alcohols:** Alkylation of **allyl phenyl sulfoxide** followed by treatement with sodium thiophenoxide or trialkylphosphite yields higher allylic alcohols in good yield.[8]



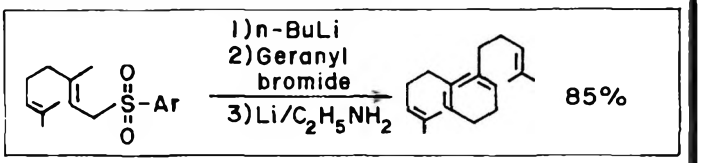
III. **Introduction of an Optically Active Center.** The methylene protons of **Benzyl methyl sulfoxide** are not equivalent, and only one is extracted to form a stable, optically active carbanion. Alkylation with a carbonyl compound and eventual displacement of the sulfur moiety provides an optically active product. The actual isomer obtained may be predicted from projection diagrams provided by Dorst, who first described this technique.[11]



IV. **1, 5-Dienes (Head to Head Coupled Allylics):** It is often useful to prepare 1, 5-dienes without disturbing the stereochemistry of the starting "ene's." Sulfonyl activated methylenes provide two timely techniques by which this may be accomplished. (A) **Methyl phenylsulfonylacetate** is alkylated with an aldehyde and then with the palladium chloride complex of an alkene. The ester and the sulfone moieties are then removed stepwise[9].



(B) **Allyl phenyl sulfone** may be alkylated with any allylhalide **(geranyl bromide, farnesyl bromide,** etc.) and the aryl sulfone removed. Larger allyl phenyl sulfones may be prepared by reacting **Benzene** or **Toluene sulfinic acid sodium salt** with the appropriate allyl halide. This technique has been used to prepare all trans Squalene in high yield[10].



1) *Tetrahedron Lett.*, 3653 (1974); **2)** *Tetrahedron Lett.*, 659 (1974); **3)** *Tetrahedron Lett.*, 1383 (1972); **4)** *J. Amer. Chem. Soc.*, 96, 1960 (1974); **5)** *J. Org. Chem.*, 40, 231 (1975); **6)** *J. Org. Chem.*, 31, 4303 (1974); **7)** *J. Org. Chem.*, 40, 1131, (1975); **8)** *J. Amer. Chem. Soc.*, 93, 4956 (1971); **9)** *J. Org. Chem.*, 40 (1975); **10)** *J. Org. Chem.*, 39, 2135 (1974); **11)** *J. Amer. Chem. Soc.*, 93, 3077 (1971). *Chem Comm.*, 1334 (1971).

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1556	1,3-Propanedithiol	9.65/25g	26.00/100g
1478	2,2'-Ethylenebis(m-Dithiane)	19.75/25g	
1238	Allyl phenyl sulfoxide	19.85/25g	61.15/100g
1318	Methyl phenylsulfonylacetate	12.95/25g	39.95/100g
1237	Allyl Phenyl sulfone	14.85/25g	45.75/100g
1479	Geranyl bromide	21.15/25g	
1480	Farnesyl bromide	13.50/10g	
2265	Benzene sulfinic acid sodium salt		10.50/100g
2266	p-Toluene sulfinic acid sodium salt		9.95/100g
1241	Benzyl methyl sulfoxide	16.95/25g	52.20/100g
2600	Farnesyl p-tolyl sulfone	11.75 5g	
2601	Geranyl p-tolyl sulfone	17.50/10g	

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AUTHOR INDEX

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Alkylidenecarbenes from Acyclic Vinyl Bromides and Potassium *tert*-Butoxide

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Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received August 29, 1975

The reaction of acyclic terminal vinyl bromides with potassium *tert*-butoxide afforded acetylenes, cyclopentenes, and lesser amounts of *tert*-butyl vinyl ethers. The reactive intermediate, an alkylidenecarbene, was seen as giving rise to the major products via two pathways: 1,5-carbon–hydrogen insertion leading to cyclopentenes and alkyl migration leading to acetylenes. In several instances 1,3-carbon–hydrogen insertion was also observed. The relative amount of 1,5-C–H insertion was found to depend on the C–H bond undergoing insertion, the ease of insertion decreasing in the order tertiary > secondary benzylic > secondary ≫ primary.

A previous report[2] from this laboratory elucidated the overall course of the reaction of terminal vinyl bromides with potassium *tert*-butoxide. The nature of the products and trapping experiments provided compelling evidence for the intermediacy of alkylidenecarbenes.

Other workers have independently reported the generation of alkylidenecarbenes.[3-9] The evidence for their claims includes trapping experiments,[3,4,6-8] dimerization,[5] and intra- and intermolecular insertions.[5,7,9] The present work was begun with the aim of providing additional information regarding the behavior of alkylidenecarbenes.

The terminal vinyl bromides employed in this study were prepared from the corresponding olefin via a bromination–dehydrobromination procedure.[10] In all cases the terminal vinyl bromide so prepared was a mixture of two geometric isomers.

The product mixtures obtained by heating vinyl bromides with potassium *tert*-butoxide at 240 °C were readily separated by GLC, and the individual components were identified on the basis of spectral data. Cyclopentene dervatives characteristically exhibit absorption near 6.1 μ in the infrared and 5.3 ppm in the NMR. Acetylenes were identified by an NMR triplet near 1.7 ppm, J = 2 Hz, which is diagnostic for a $-CH_2C{\equiv}C-CH_3$ type methyl group. *tert*-Butyl vinyl ethers can be recognized by their infrared absorption at 6.0 and 8.7 μ, NMR signals at 5.9 (–C=CHO–) and 1.2 ppm, and a substantial P − 56 ion in their mass spectra.

The major products isolated from the reaction of vinyl bromides **1**, **2**, **3**, and **4** with potassium *tert*-butoxide at 240 °C are illustrated in Chart I. The same proportion of products were obtained from fractions of **1** rich in the *E* or *Z* isomers, indicating that the products are not determined by the geometry of the starting material.

Although 1,4-dimethylcyclopentene could have been one of the three minor unidentified materials observed by GLC (8% total), it is not among the major products from vinyl bromide **4**. This demonstrates that 1,5 insertion into an unactivated primary C–H bond is not a major reaction of alkylidenecarbenes. Such behavior is in marked contrast to alkylcarbenes, which readily undergo intramolecular insertion into primary C–H bonds.[11]

Table I. Ratio of 1,5-Carbon–Hydrogen Insertion to 1,2-Alkyl Migration in the Reaction of Vinyl Bromides with Potassium *tert*-Butoxide

Vinyl bromide	H–C-5 bond type	1,5 insertion/ alkyl migration	Per H
4	Primary	0.05[a]	0.01
3	Secondary	1.13	0.28
2	Secondary	0.67	0.33
1	Tertiary	2.4	2.4

[a] Estimated assuming the formation of 3% of 1,5-insertion product, 1,4-dimethylcyclopentene.

Table I compares the relative amount of 1,5 C–H insertion as a function of the C-5 hydrogen bond type. It is clear that 1,5 insertion into a tertiary C–H bond is favored over insertion into a secondary C–H bond. The selectivity of alkylidenecarbenes is to be contrasted with alkylcarbenes whose insertion reactions are statistical,[11] or show only a slight degree of selectivity.[12]

Simple acyclic carbenes are reported to undergo intramolecular insertion via a 1,3 route to form cyclopropanes.[11] In the case of large ring carbenes, both 1,5- and 1,6-insertion reactions have been observed.[13] When a choice is possible, 1,5 insertion is favored over, but does not exclude, 1,6 insertion. The action of potassium *tert*-butoxide on 1-bromo-2,6-dimethyl-1-heptene (**2**) was examined since 1,6 insertion would occur at a tertiary center, whereas 1,5 insertion would necessitate attack at a secondary position. The reaction produced no detectable amount of 1,3,3-trimethylcyclohexene.[14] The isolation of 17% of 3-isopropyl-1-methylcyclopentene (**5**) suggests that whatever the reason for the preference for 1,5 insertion, it is more important in determining the overall course of carbon–hydrogen in-

Chart I

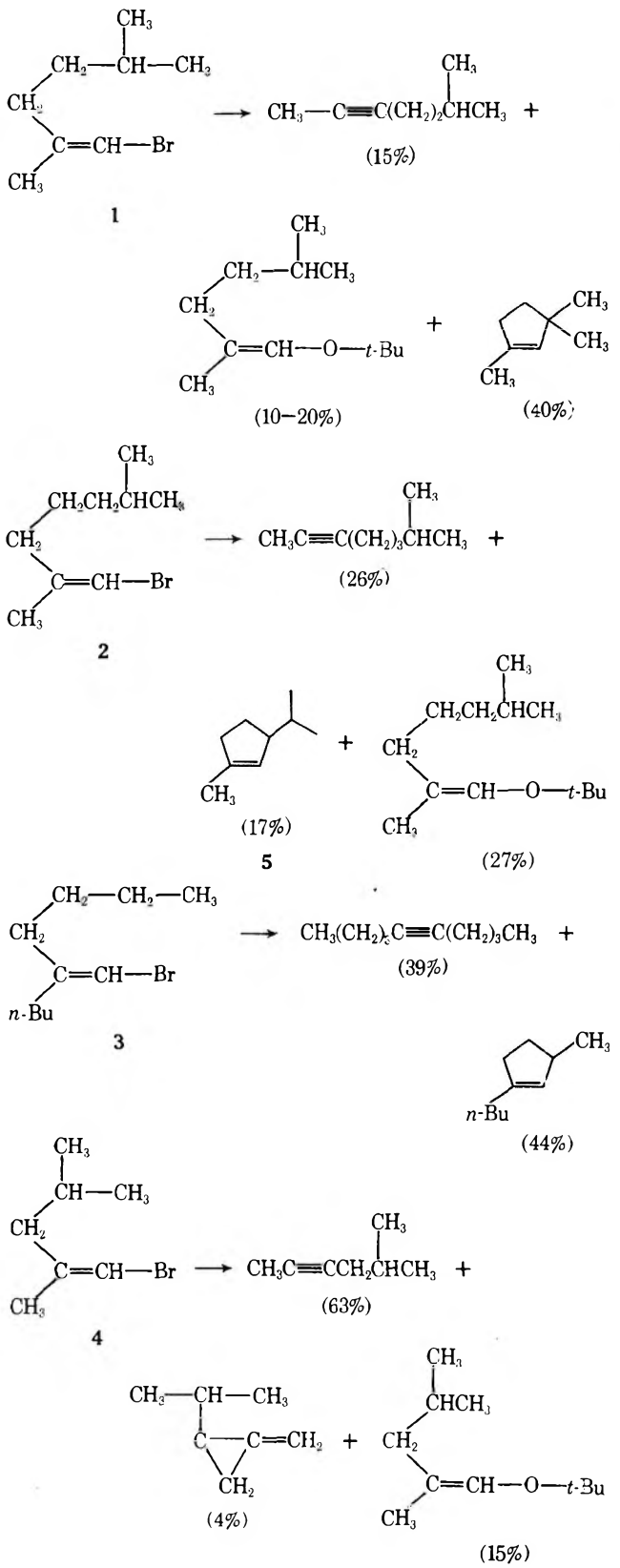
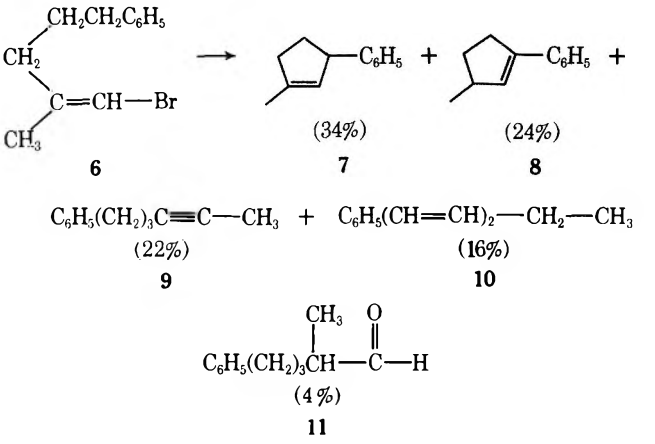


Chart II



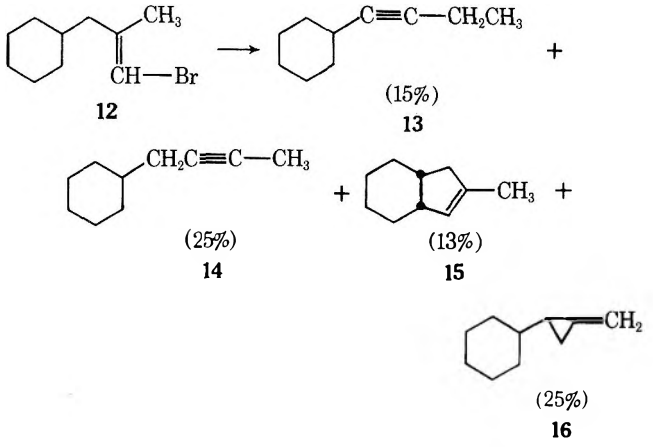
sertion than is the nature of the C–H bond undergoing insertion.

A series of reactions of 1-bromo-2,6-dimethyl-1-heptene (**2**) with potassium *tert*-butoxide carried out at temperatures ranging from 50 to 240 °C (see Experimental Section, Table IV) demonstrated that the product spread was insensitive to changes in temperature.

1-Bromo-2-methyl-5-phenyl-1-pentene (**6**) reacts with potassium *tert*-butoxide to give the product mixture illustrated in Chart II. 2-Methyl-5-phenylpentanal (**11**) most likely arises by hydrolysis of the vinyl ether normally produced in these reactions. 1-Phenyl-3-methylcyclopentene (**8**) and 1-phenyl-1,3-hexadiene (**10**) are most likely formed by base-catalyzed isomerization of the initially formed cyclopentene (**7**) and acetylene **9**, respectively.

Comparison of the total amount of cyclopentene derivatives formed by 1,5 insertion (58%) to the total amount of products produced by alkyl migration (38%) suggests that a secondary benzylic C–H is intermediate in reactivity between a secondary and tertiary C–H bond. This enhanced reactivity is also contrary to the observation that alkyl carbenes form cyclopropanes with increased difficulty when insertion occurs at a benzylic C–H bond.[15]

The reaction of 1-bromo-2-methyl-3-cyclohexyl-1-propene (**12**) with potassium *tert*-butoxide afforded 1-cyclohexyl-1-butyne (**13**), 1-cyclohexyl-2-butyne (**14**), *cis*-8-methylbicyclo[4.3.0]non-7-ene (**15**), and 2-cyclohexyl-1-methylenecyclopropane (**16**). The identity of **15** was established by comparison with an authentic sample. The major hydrocarbon product, **16**, exhibited infrared absorption at 5.8[16] and 11.2 μ and a terminal methylene signal at 5.3 ppm[17] in the NMR. The structure of **16** was confirmed by an independent synthesis from cyclohexylallene.



Methylenecyclopropane **16**[18] most likely forms by way of a 1,3 insertion followed by isomerization of the resulting cyclopropene derivative.[21] Methylenecyclopropanes are also minor products in the reaction of **1**, **2**, and **4**. There is no apparent reason for the dominant formation of **16** in the reaction of **12**.

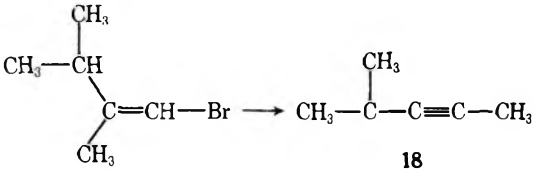
An attempt to maximize cyclopropane formation by making available a tertiary C–H bond for 1,3 insertion failed as the only hydrocarbon obtained in sufficient quan-

Table II. Properties of Vinyl Bromides[a,g]

Bromide	Bp, °C (mm)	n^{20}D	Mass spectrum,[h] *m/e* (rel intensity)
1	78–81 (23)		190* (11), 133* (7), 111 (30), 95 (15), 69 (100), 57 (51), 56 (93), 55 (64)
2[b]	44–45 (1)	1.4648	204* (7), 183 (20), 125 (7), 83 (20), 82 (13), 70 (16), 69 (100), 57 (10), 56 (11), 55 (34)
4	43–44 (7.5)	1.4631	176* (21), 134* (31), 97 (84), 56 (26), 55 (68), 53 (26), 43 (100)
3[c]	40–41.5 (0.3)		218* (18), 134* (26), 97 (23), 83 (26), 81 (17), 69 (20), 67 (23), 57 (15), 56 (66), 55 (92), 41 (100)
6[d]	116–118 (1.7)	1.5412	238* (6), 159 (9), 117 (16), 105 (28), 104 (100), 92 (23), 91 (69), 77 (17), 65 (25), 53 (24)
19[e]	102–103 (10)	1.5602	210* (22), 131 (32), 129 (40), 128 (33), 116 (56), 115 (100), 91 (95), 89 (26), 77 (26), 65 (31), 64 (21), 63 (46)
12[f]	96–98 (5.5)		216* (9), 83 (85), 82 (47), 81 (27), 67 (21), 55 (100), 54 (10), 53 (17)
17	47–48 (24)		162* (34), 147 (17), 85 (35), 83 (100), 67 (84), 65 (17), 55 (83), 53 (21)

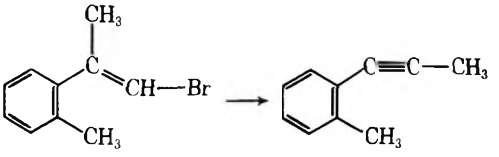
[a] The vinyl bromides described above showed an ir band at 6.12–6.18 μ and NMR signals for the $CH_3C{=}C$ between 1.75 and 1.78 ppm and for C=CH at 5.84–5.90 ppm. [b] NMR and GLC analysis indicated a cis/trans ratio of 2:3. [c] 2-Butyl-1-hexene was prepared by the reaction of 5-nonanone with methylenetriphenylphosphorane in refluxing ether for 2 days followed by replacement of the ether with THF and heating for an additional 6 days. [d] The reaction of methyllithium with 4-phenylbutyric acid gave 5-phenylpentan-2-one, bp 92–93 °C (2 mm, n^{20}D 1.5094. A Wittig reaction converted this ketone to 2 methyl-5-phenyl-1-pentene. [e] An attempt to purify the intermediate dibromide by distillation led to dehydrobromination and the formation of allyl bromide (75%) and vinyl bromide (25%). [f] 2-Methyl-3-cyclohexyl-1-propene was prepared in 78% yield by a Wittig reaction using cyclohexylacetone. [g] Satisfactory analytical data (±0.3% for C, H) for all compounds listed were submitted for review. [h] An asterisk indicates presence of bromine.

tity for identification from the reaction of 1-bromo-2,3-dimethyl-1-butene (17) was 4-methyl-2-pentyne (18).



17 18

Finally, the reaction of 1-bromo-2-(*o*-tolyl)-1-propene (19) with potassium *tert*-butoxide gave 93% of 1-(o-tolyl)-1-propyne (20), demonstrating that C–H insertion does not compete with the extremely rapid[8b] 1,2 migration of an aryl group.



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Experimental Section[22]

General Procedure for the Preparation of Vinyl Bromides. 1-Bromo-2,5-dimethyl-1-hexene (1). To a solution of 10.0 g (0.079 mol) of 2,5-dimethyl-1-hexene in 100 ml of hexane and 4 ml of pyridine at 0 °C was slowly added 12.8 g (0.080 mol) of bromine. The mixture was then stirred at ambient temperature for 30 min. The solution was decanted from the yellow solid and washed with 150 ml of 5% aqueous sodium bicarbonate and 100 ml of saturated sodium chloride solution. The solution was dried ($MgSO_4$) and evaporated under diminished pressure to afford 20.9 g of 1,2-dibromo-2,5-dimethylhexane which was dissolved in 50 ml of ethanol containing 4.5 g (0.080 mol) of potassium hydroxide. After stirring for 16 h at ambient temperature the solution was diluted with water and extracted with ether. The ether solution was washed with saturated salt solution and dried ($MgSO_4$). Distillation gave 13.2 g of 1-bromo-2,5-dimethyl-1-hexene, bp 78–81° (23 mm). The presence of *Z* and *E* isomers (35:65 ratio) was revealed by GLC using a SE-30 column. An analytical sample containing both isomers was obtained by GLC using a 20% Carbowax column at 140°. For properties and NMR shifts of vinyl bromides, see Tables II and III.

General Procedure for Reaction of Vinyl Bromides with Potassium *tert*-Butoxide. A. 1-Bromo-2,5-dimethyl-1-hexene (1). A 2.0-g (0.018 mol) sample of potassium *tert*-butoxide (MSA Research Corp.) was added to a 50-ml side-armed flask, capped with a stoppule and equipped with a distillation head leading to a pair of dry ice–isopropyl alcohol cooled traps whose exit was protected by a calcium chloride drying tube. A slow stream of nitrogen was passed through the system throughout the course of the reaction. The flask was heated to 240° employing a silicone oil bath and then 3.0 g (0.016 mol) of 1-bromo-2,5-dimethyl-1-hexene (1) was injected, using a syringe via the side arm under the surface of the hot potassium *tert*-butoxide. The flask was heated for another 1 min and allowed to cool to room temperature. Water was added and the mixture extracted with ether. The ether was combined with the ether washings from the two traps and the resulting solution was washed with water and dried ($MgSO_4$). The ether was carefully distilled to leave 1.52 g of liquid whose analysis by GLC (20% Carbowax, 125°) showed the presence of at least six components.

Component 1 (retention time 1.6 min, 36%) was identified as 1,3,3-trimethylcyclopentene: ir (CCl_4) 3.40, 6.09, 6.91, 7.31, 7.40, and 8.99 μ; NMR (CCl_4) 0.99 [s, 6, $(CH_3)_2C$–]; 1.65 (d, 5, J = 1 Hz, $CH_3C{=}CH$– superimposed on $-CH_2-$), 2.24 (distorted t, 2, $-CH_2CH_2C{=}C-$), and 5.05 ppm (m, 1, C=CH–); mass spectrum (70 eV) *m/e* (rel intensity) 110 (13), 95 (100), 67 (17).

Component 2 (retention time 3.9 min, 15%) was identified as 6-methyl-2-heptyne: ir (CCl_4) 3.40, 6.92, 7.24, 7.33, 7.60, and 8.59 μ; NMR (CCl_4) 0.88 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.39 (m, 2, $-CH_2-$), 1.72 (t, 4, J = 2 Hz, $CH_3C{\equiv}C-CH_2-$ superimposed on CH), and 2.09 ppm (m, 2, $-CH_2C{\equiv}C-$); mass spectrum (70 eV) *m/e* (rel intensity) 110 (3), 95 (72), 81 (10), 67 (33), 65 (58), 55 (22), 53 (58), 52 (20), 51 (32), 43 (25), 41 (95), and 39 (100).

Table III. NMR Shifts for *gem*-Dimethyl Groups of Vinyl Bromides

$(CH_3)_2CH(CH_2)_n$—C(CH$_3$)=CHBr

n	δ_{trans}, ppm	δ_{cis}, ppm[a]	Δ, ppm
0	0.96	1.07	0.11
1	0.88	0.93	0.05
2	0.92	0.95	0.03
3	0.89	0.89	0.00

[a] The stereochemistry was assigned on the basis that the bromine should deshield the cis *gem*-dimethyl group. The *E* isomers were also shown to be the less volatile[7] by GLC.

Table IV. Temperature Dependence of the Reaction of 1-Bromo-2,6-dimethyl-1-heptene (*2*) with Potassium *tert*-Butoxide

Temp, °C	1-Methyl-3-isopropylcyclopentene	7-Methyl-2-octyne	1-*tert*-Butoxy-2,6-dimethyl-1-heptene
240	30	45	25
200	29	45	26
160	33	40	26
100	38	37	26
50	33	34	34

Component 3 (retention time 8.2 min, 7%) was identified as one of the isomeric 1-*tert*-butoxy-2,5-dimethyl-1-hexenes, ir 6.00 and 8.70 μ.

Component 4 (retention time 10 min, 5%) was the other geometric isomer of 1-*tert*-butoxy-2,5-dimethyl-1-hexene: ir 5.98 and 8.70 μ; NMR (CCl_4) 0.88 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.20 [s, 9, $(CH_3)_3CO$–], 1.50 (d, 3, CH_3C=CH–), 1.80 (m, 2, –CH_2C=C–), and 5.91 ppm (m, 1, C=CHO–); mass spectrum *m/e* (rel intensity) 184 (15), 128 (48), 110 (46), 99 (30), 95 (53), 85 (29), 72 (15), 71 (100), 69 (26), 68 (15), 59 (16), 58 (28), 57 (95), 56 (27), 55 (30), 43 (63), 41 (69), 39 (27).

Components 5 and 6 (retention time 13.1 and 14.9 min, 39%) were the starting vinyl bromides. The relative proportions of the two vinyl bromides were essentially identical with the proportions present in the original starting material.

When the experiment was repeated using 4.5 equiv of potassium *tert*-butoxide the proportion of vinyl ethers rose to 20% and the amount of recovered vinyl bromides dropped to 7%. The use of vinyl bromide fractions with differing isomeric composition resulted in identical product spreads.

B. 1-Bromo-2,6-dimethyl-1-heptene (2). Treatment of 3.22 g (0.016 mol) of 1-bromo-2,6-dimethyl-1-heptene (**2**) with 2.0 g (0.018 mol) of potassium *tert*-butoxide as previously described gave 1.85 g of crude product whose analysis by GLC (Carbowax, 110°) indicated the presence of seven components (Table IV).

Component 1 (retention time 2.6 min, 4%) was too volatile to collect.

Component 2 (retention time 4.6 min, 17%) proved to be a mixture of two components. This fraction was collected and then rechromatographed on a freshly prepared Carbowax column at 80 °C. Approximately 90% of this mixture was identified as 1-methyl-3-isopropylcyclopentene: ir (CCl_4) 6.08 μ; NMR (CCl_4) 0.87 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.72 (s, 3, CH_3C=C–), and 5.27 ppm (m, 1, CH=C–); mass spectrum *m/e* (rel intensity) 124 (11), 109 (6), 82 (7), 81 (100), 80 (8), 79 (10), 69 (7), 67 (5), 53 (5) and 41 (10). The remaining 10% of this fraction was collected and identified as 2-isoamylmethylenecyclopropane: ir (CCl_4) 3.40, 5.80 (w), 6.85, 7.26, 7.35, 8.89, and 11.24 μ (s). This infrared spectrum was identical with that of isoamylmethylenecyclopropane prepared by an independent route.[23]

Component 3 (retention time 10.3 min, 26%) was identified as 7-methyl-2-octyne: ir 4.90 μ (w); NMR (CCl_4) 0.89 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.1–1.6 (m, 5, –CH_2CH_2CH–), 1.72 (t, 3, J = 2.2 Hz, CH_3C≡C–CH_2–), and 2.04 ppm (m, 2, –CH_2C≡C–); mass spectrum *m/e* (rel intensity) 124 (0.1), 109 (100), 81 (30), 69 (70), 68 (37), 67 (43), 55 (28), 54 (16), 53 (12), 43 (43), and 39 (19).

Anal. Calcd for C_9H_{16}: C, 87.04; H, 12.98. Found: C, 87.29; H, 13.12.

Components 4 and 5 (retention times 25 and 28 min, 27%) were identified as geometric isomers of 1-*tert*-butoxy-2,6-dimethyl-1-heptene contaminated with a small amount of 2,6-dimethylheptanal: ir 5.80 (w) and 5.99 μ; NMR (CCl_4) 0.88 [d, 6, $(CH_3)_2CH$–], 1.20 [s, –$OC(CH_3)_3$], 5.90 (m, –C=CHO–), and 9.50 ppm (–CHO).

Components 6 and 7 (retention times 32 and 35 min, 27%) proved to be the original vinyl bromides.

The GLC retention time of an authentic sample of 1,3,3-trimethylcyclohexene[14] was found to be different from that of component 1 and did not correspond with any of the significant peaks found in the product mixture described above.

C. 1-Bromo-2,4-dimethyl-1-pentene (4). The reaction of 3.0 g (0.017 mol) of 1-bromo-2,4-dimethyl-1-pentene (**4**) with 2.0 g (0.018 mol) of potassium *tert*-butoxide gave 1.3 g of light brown liquid which was separated using a 20% Carbowax column at 104°. The first fraction (retention time 1.5–[2.5 min, 12%) was a mixture of at least four components. Infrared absorption at 5.82 and 11.30 μ and an NMR signal at 5.3 ppm suggested that one of these components was 2-isopropyl-1-methylenecyclopropane. The mass spectrum of a carefully collected sample of this 4% component showed a molecular ion at *m/e* 96 (33%) and a base peak at *m/e* 81.

The second fraction (retention time 3.3 min, 63%) was identified as 5-methyl-2-hexyne: NMR (CCl_4) 0.93 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.73 (t, 3, J = 2.2 Hz, CH_3C≡C–CH_2–), and 1.95 ppm (m, 2, –CH_2C≡C–); mass spectrum *m/e* (rel intensity) 96 (100), 81 (75), 79 (15), 68 (11), 67 (12), 55 (15), 54 (48), 53 (34), 51 (13), 43 (53), 41 (40), 39 (36), and 27 (24).

Fraction 3 (retention time 8.9 min, 3%) was identified as one of the isomeric 1-*tert*-butoxy-2,4-dimethyl-1-pentenes: ir 5.99, 8.09, and 8.70 μ.

Fraction 4 (retention time 9.2 min, 12%) was identified as the other geometric isomer of 1-*tert*-butoxy-2,4-dimethyl-1-pentene: ir 5.99, 8.09, and 8.70 μ; NMR (CCl_4) 0.85 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$–], 1.20 [s, 9, $(CH_3)_3CO$], 1.50 (d, 3, J = 1 Hz, CH_3C=CH–), 1.72 (m, 3), and 5.90 ppm (m, 1, –C=CHO); mass spectrum *m/e* (rel intensity) 170 (8), 114 (35), 71 (100), 57 (37), 55 (14), 43 (40), 41 (33), and 39 (11).

Fraction 5 (retention time 12.2 min, 10%) proved to be unreacted vinyl bromide.

D. 1-Bromo-2-*n*-butyl-1-hexene (3). Treatment of 2.19 g (0.01 mol) of 1-bromo-2-*n*-butyl-1-hexene (**3**) with 3.40 g (0.03 mol) of potassium *tert*-butoxide gave 1.2 g of yellow liquid. Separation by GLC (20% Carbowax, 113 °C) revealed the presence of five major components. Component 1 (retention time 5 min, 44%) was identified as 1-*n*-butyl-3-methylcyclopentene: ir 6.10 μ; NMR (CCl_4) 0.98 (d, 3, J = 6.5 Hz, –$CHCH_3$), 1.0–1.7 (m, 7, –$CH_2CH_2CH_3$), 1.9–2.4 [m, 4, (–CH_2)$_2$C=C–], 2.67 (m, 1, CHC=C–), and 5.19 ppm (m, 1, –CH=C–); mass spectrum *m/e* (rel intensity) 138 (39), 93 (28), 82 (25), 81 (100), 79 (27), 67 (35), 55 (39), and 41 (43).

Component 2 (retention time 7 min, 6%) was an allene,[26] ir 5.11 μ.

Component 3 (retention time 9 min, 39%) was identified as 5-decyne:[27] ir 3.40, 6.85, 7.29, and 10.21 μ; NMR (CCl_4) 0.91 (dist t, 6, –CH_2CH_3), 1.44 (m, 8, –CH_2–), 2.10 ppm (dist t, 4, –CH_2C≡C–CH_2–). This compound and an authentic sample of 5-decyne[28] showed identical retention times on Carbowax and tricresyl phosphate columns. Catalytic hydrogenation of component 3 gave a product whose mass spectrum was identical with that of *n*-decane.

Component 4 (retention time 14 min, 10%) was not identified, ir 6.05 μ, molecular ion at *m/e* 184.

Component 5 (retention time 24 min, 9%) was not identified, ir strong 9.10 μ, molecular ion at *m/e* 184.

E. 1-Bromo-2-methyl-5-phenyl-1-pentene (6). The reaction of 1.60 g (6.7 mmol) of 1-bromo-2-methyl-5-phenyl-1-pentene (**6**) with 1.03 g (9.2 mmol) of potassium *tert*-butoxide gave 0.95 g of crude product which was separated using a 20% Carbowax column at 200°. Component 1 (retention time 13.6 min, 34%) was identified as 1-methyl-3-phenylcyclopentene (**7**): ir 6.02, 6.24, and 6.70 μ; NMR (CCl_4) 1.81 (broad s, 3, CH_3C=C–), 1.5–2.7 (m, 4, –CH_2CH_2–), 3.85 (m, 1, C=C–CHC_6H_5), 5.35 (m, 1, C=CH–), and 7.10 ppm (s, 5, ArH); mass spectrum *m/e* (rel intensity) 158 (24), 143 (70), 128 (75), 115 (87), 105 (26), 102 (32), 91 (100), 78 (55), 77

(94), 65 (54), 63 (61), 52 (34), 51 (65), 50 (66), 43 (36), 41 (61), and 39 (43).

Component 2 (retention time 19.3 min, 22%) was identified as 6-phenyl-2-hexyne (**9**):[29] ir 3.30, 3.41, 6.26, 6.71, 6.91, 9.23, and 9.66 μ; NMR (CCl_4) 1.75 (t, 3, J = 2.2 Hz, $CH_3C{\equiv}C-CH_2-$), 2.1 (m, 4, $-CH_2CH_2-$), 2.68 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2-$), and 7.13 ppm (m, 5, C_6H_5-); mass spectrum m/e (rel intensity) 158 (43), 143 (55), 130 (28), 129 (55), 128 (25), 105 (31), 104 (100), 92 (29), 91 (99), 77 (24), and 65 (27).

Component 3 (retention time 20.8 min, 24%) was identified as 1-phenyl-3-methylcyclopentene (**8**) ir 6.15, 6.26, and 6.71 μ; NMR (CCl_4) 1.10 (d, 3, J = 6.5 Hz, CH_3CH-), 6.01 (m, 1, $C_6H_5C{=}CH$), and 7.23 ppm (m, 5, C_6H_5-); mass spectrum m/e (rel intensity) 158 (14), 143 (47), 129 (38), 128 (70), 115 (100), 102 (34), 91 (42), 78 (38), 77 (63), 65 (33), 63 (55), 51 (93), 50 (59), 41 (34), 39 (38), and 27 (31).

Component 4 (retention time 28 min, 16%) was identified as 1-phenyl-1,3-hexadiene (**10**): ir 3.30, 3.40, 5.96, 6.11, 6.30, 6.71, 7.71, 9.32, 9.71, 10.15, and 10.99 μ; uv (EtOH) λ_{max} 285 nm (ϵ 2 × 10^4); NMR 1.04 (t, 3, J = 6.5 Hz, CH_3CH_2-), 2.17 (m, 2, $C{=}C-CH_2-$), 5.9, 6.4, and 7.2 ppm (m's, 9, $C_6H_5CH{=}CHCH{=}CH-$); mass spectrum m/e (rel intensity) 158 (46), 143 (36), 131 (24), 129 (100), 128 (51), 115 (22), 91 (17), and 77 (19).

Component 5 (retention time 40.5 min, 4%) was identified as 2-methyl-5-phenylpentenal (**11**): ir (CCl_4) 3.33, 3.45, 3.75, 5.75, 6.25, and 6.70 μ.

F. 1-Bromo-2-methyl-3-cyclohexylpropene (12). The reaction of 1.37 g of 1-bromo-2-methyl-3-cyclohexylpropene with 0.71 g of potassium *tert*-butoxide gave 0.95 g of crude product which was separated using a 20% Carbowax column at 130°. The first component (retention time 4.5 min 39%) proved to be a mixture of two olefins which was separated by rechromatography employing a freshly prepared 20% carbowax column. The major olefin (65%) was identified as 2-cyclohexylmethylenecyclopropane (**16**): ir (CCl_4) 3.40, 5.82 (w), and 11.23 μ; NMR (CCl_4) 1.1–1.7 (m, 14) and 5.30 ppm (m, 2, $-C{=}CH_2$); mass spectrum m/e (rel intensity) 136 (5), 121 (46), 107 (21), 94 (30), 93 (53), 81 (100), 80 (31), 79 (54), 67 (32), 55 (21), 41 (33), and 39 (24). This compound was identical in all respects with a sample of 2-cyclohexylmethylenecyclopropane prepared by an independent method. The minor olefin (35%) in the first fraction was identified as *cis*-8-methylbicyclo[4.3.0]non-7-ene (**15**) on the basis of the following spectral data and by comparison with an authentic sample prepared by an independent route: ir (CCl_4) 3.29, 3.40, and 6.10 μ; NMR (CCl_4) 1.39 (m, 8), 1.70 (d, 3, J = 1 Hz, $CH_3C{=}C-$), 1.9–2.7 (m, 4), and 5.22 ppm (m, 1, $C{=}CH-$); mass spectrum m/e (rel intensity) 136 (45), 121 (100), 107 (18), 94 (56), 93 (83), 91 (23), 81 (21), 80 (22), 79 (51), 77 (25), 67 (15), 41 (17), and 39 (16).

Fraction 2 (retention time 6.4 min, 15%) was identified as 1-cyclohexyl-1-butyne (**13**): ir (CCl_4) 3.39 and 5.09 μ; NMR (CCl_4) 1.10 (t, 3, J = 7 Hz, $-CH_3$), 2.10 (q, 2, J = 7 Hz, $-CH_2-$), and 0.8–2.0 ppm (broad m); mass spectrum m/e (rel intensity) 136 (59), 121 (31), 107 (67), 94 (32), 93 (48), 91 (30), 82 (20), 81 (45), 80 (20), 79 (100), 77 (29), 68 (26), 67 (46), 55 (27), and 41 (28).

Fraction 3 (retention time 9.8 min, 25%) was identified as 1-cyclohexyl-2-butyne (**14**): ir 3.41 and 6.90 μ; NMR (CCl_4) 0.8–1.6 (m, 10), 1.71 (t, 3, J = 2 Hz, $-CH_3$), and 1.90 ppm (m, 3, $-CH-$ and $-CH_2-$); mass spectrum m/e (rel intensity) 136 (39), 121 (34), 107 (42), 94 (36), 93 (20), 83 (76), 82 (49), 81 (31), 79 (21), 67 (40), 55 (100), and 41 (31).

Fraction 4 (retention time 17.2 min, 21%) was identified as a mixture of 1-t-butoxy-2-methyl-3-cyclohexylpropene (ir absorption at 6.0 and 8.7 μ) and an unidentified impurity which was present in the original vinyl bromide.

***cis*-8-Methylenebicyclo[4.3.0]nonane.** A 6.2-g sample of 2-indanone was hydrogenated in ethanol using platinum oxide as catalyst (3 days). The catalyst was removed and the filtrate added to water and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated. The residue was taken up in acetone and treated with chromic acid in sulfuric acid–water. The usual work-up gave 5 g of a mixture which was largely *cis*-bicyclo[4.3.0]nonan-8-one. A GLC sample of the ketone showed ir 5.73 μ; NMR 1.3–1.6 (m, 8), 1.9–2.4 ppm (broad with sharp spike at 2.09, 6); mass spectrum m/e 138 (32).

To a solution of methylenetriphenylphosphorane (prepared from 10.8 g of methyltriphenylphosphonium bromide and 11.4 ml of 2.25 M butyllithium in hexane) was added 4.62 g of the crude ketone. The mixture was refluxed for 15 h, 75 ml of dry THF was added, and heating was continued for 24 h, after which 25 ml of dimethyl sulfoxide was added and the mixture was heated at reflux for an additional 36 h. Work-up in the usual manner gave 1.87 g of a liquid which was found to be a four-component mixture by GLC using a 20% Carbowax column at 210°. The four components were separated by preparative GLC. Component 1 (retention time 4 min, 23%) was identified as *cis*-bicyclo[4.3.0]nonane, NMR (CCl_4) two envelopes at 1.57 and 1.40 ppm. Component 2 (retention time 5.5 min, 18%) was identified as *cis*-8-methylenebicyclo[4.3.0]nonane: ir (CCl_4) 3.23, 3.42, 6.03, and 11.33 μ; NMR (CCl_4) 1.41 (m, 8), 2.15 (m, 6), and 4.81 ppm (quintet, 2, $C{=}CH_2$). Component 3 (retention time 8 min, 14%) was identified as indan: NMR (CCl_4) 2.04 (quintet, 2), 2.83 (t, 4), and 7.05 ppm (m, 4, ArH). Component 4 (retention time 23.5 min, 44%) was identified as *cis*-bicyclo[4.3.0]nonan-8-one.

***cis*-8-Methylbicyclo[4.3.0]non-7-ene (15).** To a solution of methylmagnesium iodide (prepared from 0.725 g of methyl iodide and 0.124 g of magnesium) in dry ether was added an ether solution of 0.7 g of *cis*-bicyclo[4.3.0]nonan-3-one. The resulting solution was heated at reflux for 2 h, and then a 2% solution of hydrochloric acid was added and the ether layer was separated, washed with 5% sodium bicarbonate solution, and dried ($MgSO_4$). The ether was removed, affording an oil which showed strong infrared absorption at 2.90 μ, in addition to weak absorption at 5.74 μ (carbonyl). The reaction mixture was dehydrated by passage through a Carbowax GLC column at 210 °C affording a broad band collected between retention times of 5 and 10 min. Analysis of this material indicated it to be mixture of *cis*-8-methylbicyclo[4.3.0]non-7-ene (80%) and *cis*-8-methylenebicyclo[4.3.0]nonane (20%). A pure sample of the major product obtained by careful GLC showed ir (CCl_4) 6.05 μ; NMR ($CDCl_3$) 1.70 (s, 3, $CH_3C{=}C-$), 2.0–2.7, and 5.27 ppm (m, 1, $CH{=}C-$).

***trans*-8-Methylenebicyclo[4.3.0]nonane.** To a suspension of 5.66 g of triphenylphosphonium bromide in ether was added 6.2 ml of a 2.25 M solution of *n*-butyllithium in hexane. An ether solution of *trans*-bicyclo[4.3.0]nonan-8-one[30] was added and the mixture was refluxed for 1 h, at which time 13 ml of Me_2SO was added. Heating was continued for 15 h and the mixture was worked up in the usual manner to afford 0.74 g (39%) of *trans*-8-methylenebicyclo[4.3.0]nonane. A pure sample isolated by GLC showed n^{20}D 1.4721 (lit.[31] n^{20}D 1.4720); ir 3.23, 3.40, and 6.00 μ; NMR (CCl_4) 1.0–2.6 (14) and 4.78 ppm (m, 2, $C{=}CH_2$).

Cyclohexylallene. Attempts to prepare cyclohexylallene by the reaction of cyclohexylmagnesium bromide or chloride with propargyl bromide gave only a small amount of allene and cyclohexyl bromide as the major product.[32] The allene was prepared in good yield from propargyl chloride as follows.

To a 0.4 M solution of cyclohexylmagnesium bromide in ether (prepared from 6.52 g of cyclohexyl bromide and 1.22 g of magnesium) was added 2.4 g of propargyl chloride in ether. Saturated ammonium chloride solution was added, the layers were separated, and the ether layer was washed with 5% sodium bicarbonate solution and water and dried ($MgSO_4$). The ether was removed to leave 2.0 g (50%) of crude cyclohexylallene, contaminated with a small amount of the isomeric terminal acetylene. An analytical sample of the allene was obtained by GLC: mass spectrum m/e (rel intensity) 122 (42), 107 (60), 93 (62), 81 (73), 80 (83), 79 (100), 77 (41), 67 (67), 55 (78), 41 (63), and 39 (65).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.66; H, 11.38.

2-Cyclohexylmethylenecyclopropane (16). A slurry of 0.6 g of active zinc–copper couple[33] in 15 ml of ether containing 2.43 of diiodomethane and a crystal of iodine was refluxed for 30 min and then 1.0 g of cyclohexylallene was added. After heating for 40 h, the reaction mixture was worked up as described in the preparation of 2-isoamylmethylenecyclopropane to afford 1.1 g of liquid which proved to be a six-component mixture by GLC analysis (SF-96 at 130 °C). The first component was the terminal acetylene contaminant in the starting allene; the second component was dioodomethane. Component 3 (retention time 16 min, 36%) was identified as unreacted allene and component 4 (retention time 22 min, 6%) was the desired 2-cyclohexylmethylenecyclopropane: ir (CCl_4) 3.25, 3.41, 5.76 (w), 11.01, and 11.24 μ; NMR (CCl_4) 5.29 ppm (m, 2, $C{=}CH_2$); mass spectrum m/e (rel intensity) 136 (1.6), 121 (50), 107 (22), 94 (29), 93 (41), 81 (100), 80 (30), 79 (52), 67 (32), 55 (23), 41 (35), and 39 (30).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.90; H, 12.00.

Component 5 (retention time 29 min, 25%) was tentatively identified as cyclohexylspiropentane: ir 3.40, 6.89, and 9.70 μ. Component 6 (retention time 35 min, 13%) was not identified.

G. 1-Bromo-2,3-dimethyl-1-butene (17). Reaction of 4.89 g of

1-bromo-2,3-dimethyl-1-butene (**17**) with 3.50 g of potassium *tert*-butoxide was carried out in the usual manner and the ether was distilled off through a 16-in. Vigreux column to afford a liquid which proved to be a seven-component mixture by GLC (20% Carbowax at 110 °C). Component 1 (retention time 3.3 min, 22%) was identified as 4-methyl-2-pentyne: ir 3.35, 6.80, 7.22, 7.33, and 7.58 μ; NMR (CCl_4) 1.10 (d, J = 6 Hz), 1.71 (d, 3, J = 2.2 Hz, $CH_3C{\equiv}C-$), and 2.50 ppm (m, 1, $-CHC{\equiv}C-$); mass spectrum *m/e* (rel intensity) 82 (69), 67 (100), 65 (22), 41 (66), and 39 (48).

Components 2 and 3 together amounted to about 4% of the product and were not further examined. Component 4 (retention time 9.5 min, 3%) was an impurity present in the starting vinyl bromide. Component 5 (retention time 12.5 min, 13%) was identified as 1-*tert*-butoxy-2,3-dimethyl-1-butene, ir (CCl_4) 6.00 and 8.70 μ. Components 6 and 7 (retention times 16.2 and 18.1 min, 56%) were unreacted vinyl bromides.

H. Reaction of 1-Bromo-2-(*o*-tolyl)propene (19). A 2.1-g sample of 1-bromo-2-(o-toly)propene (**19**) was treated with 1.3 g of potassium *tert*-butoxide to yield 1.25 g of crude product. GLC analysis using a Carbowax column at 180 °C showed the material to be an eight-component mixture; however, one component comprised 93% of the mixture and the largest of the remaining seven amounted to 2%. The major component, 1-(o-tolyl)-1-propyne (**20**), was isolated by GLC and showed ir 4.42, 6.26, and 6.73 μ; NMR (CCl_4) 2.05 (s, 3, $CH_3C{\equiv}CAr$), 2.38 (s, 3, CH_3Ar), and 6.9–7.3 ppm (m, 4, ArH); mass spectrum *m/e* (rel intensity) 130 (100), 129 (57), 128 (48), 127 (23), and 115 (56). None of the minor products were examined.

Registry No.—(*E*)-**1**, 57496-96-5; (*Z*)-**1**, 57496-97-6; (*E*)-**2**, 57496-98-7; (*Z*)-**2**, 57496-99-8; **3**, 54265-12-2; (*E*)-**4**, 57497-00-4; (*Z*)-**4**, 57497-01-5; **5**, 13828-12-1; **6**, 57497-02-6; **7**, 57497-03-7; **8**, 57497-04-8; **9**, 34298-75-4; **10**, 41635-77-2; **11**, 36613-11-3; **12**, 57497-05-9; **13**, 57497-06-0; **14**, 57497-07-1; **15**, 57497-08-2; **16**, 57497-09-3; (*E*)-**17**, 57497-10-6; (*Z*)-**17**, 57497-11-7; **18**, 21020-27-9; **19**, 57497-12-8; **20**, 57497-13-9; 4-phenylbutyric acid, 1821-12-1; 5-phenyl-2-pentanone, 2235-83-8; 2-methyl-5-phenyl-1-pentene, 6683-49-4; 2-methyl-3-cyclohexyl-1-propene, 3990-93-0; cyclohexylacetone, 103-78-6; 2,5-dimethyl-1-hexene, 6975-92-4; bromine, 7726-95-6; 2,6-dimethyl-1-heptene, 3074-78-0; 2,4-dimethyl-1-pentene, 2213-32-3; 2-o-tolylpropene, 7399-49-7; 2,3-dimethyl-1-butene, 563-78-0; potassium *tert*-butoxide, 865-47-4; 1,3,3-trimethylcyclopentene, 57497-14-0; 6-methyl-2-heptyne, 51065-64-6; (*E*)-1-*tert*-butoxy-2,5-dimethyl-1-hexene, 57497-15-1; (*Z*)-1-*tert*-butoxy-2,5-dimethyl-1-hexene, 57497-16-2; 2-butyl-1-hexene, 6795-79-5; 2-isoamylmethylenecyclopropane, 57497-17-3; 7-methyl-2-octyne, 57497-18-4; (*E*)-1-*tert*-butoxy-2,6-dimethyl-1-heptene, 57497-19-5; (*Z*)-1-*tert*-butoxy-2,6-dimethyl-1-heptene, 57497-20-8; 2-isopropyl-1-methylenecyclopropane, 57497-21-9; 5-methyl-2-hexyne, 53566-37-3; (*Z*)-1-*tert*-butoxy-2,4-dimethyl-1-pentene, 57497-22-0; (*E*)-1-*tert*-butoxy-2,4-dimethyl-1-pentene, 57497-23-1; 1-*n*-butyl-3-methylcyclopentene, 57497-24-2; 5-decyne, 1942-46-7; *cis*-8-methylenebicyclo[4.3.0]nonane, 57497-25-3; 2-indanone, 615-13-4; *cis*-bicyclo[4.3.0]nonan-8-one, 5689-04-3; *cis*-bicyclo[4.3.0]nonane, 4551-51-3; indan, 496-11-7; *trans*-8-methylenebicyclo[4.3.0]nonane, 57497-26-4; *trans*-bicyclo[4.3.0]nonan-8-one, 16484-17-6; cyclohexyl bromide, 108-85-0; cyclohexyl chloride, 542-18-7; propargyl bromide, 106-96-7; propargyl chloride, 624-65-7; cyclohexylallene, 5664-17-5; cyclohexylspiropentane, 57497-27-5; 5-nonanone, 502-56-7.

References and Notes

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Carbon-13 Nuclear Magnetic Resonance Studies of Benzocycloalkenes and Fluorobenzocycloalkenes[1]

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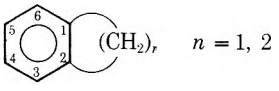
The ^{13}C NMR spectra of *o*-xylene, tetralin, indan, benzocyclobutene, and *o*-di-*tert*-butylbenzene and (excluding the latter) their 3- and 4-fluoro analogues have been obtained and assigned. In the hydrocarbon cases, aromatic carbon assignments were confirmed by examination of tactically deuterated compounds, while considerations of ^{13}C–^{19}F couplings and ^{19}F contributions to carbon screenings permitted complete assignments of all aryl and essentially all aliphatic carbon signals in the fluorobenzocycloalkenes. It is concluded that fluoro substitution in aromatic systems is manifested by sufficiently regular trends in ^{13}C–^{19}F couplings and contributions to carbon screenings as to be a useful strategy for spectral assignment of the unfluorinated aromatic. Trends in chemical shifts with the size of the fused ring ("ring stain") are discussed in the light of existing chemical shift theory, and available quantum chemical calculations for these systems. Some examination of the ^{1}H NMR spectra of the deuterated benzocycloalkenes and ^{13}C satellite spectra have been conducted and while confirming the previous proton assignments for indan demand reversal of the assignments for o-di-*tert*-butylbenzene and benzocyclobutene. Preliminary studies of relaxation phenomena in these systems (T_1 measurements) indicate a useful basis for spectral assignments, as C_α in all cases examined has a longer T_1 than C_β. A qualitative explanation in terms of preferred modes of molecular rotation is advanced.

Much effort has been expended in determining the chemical and physical properties of benzocycloalkenes (I) since the initial observations of Mills and Nixon some 45 years ago.[3a,b]



I

Changes in properties at positions in the aromatic ring are usually associated with "ring strain" effects as the size of the 1,2-fused ring decreases, and a number of explanations involving bond fixation,[3a,b] bond-order changes[4] in intermediates in electrophilic substitutions, orbital electronegativities,[5] etc., have been advanced. Direct evidence of the effects of strain on molecular properties[6] of unsubstituted benzocycloalkenes is not abundant, but Gunther's liquid crystal ^{1}H NMR studies[7] of benzocyclopropene (n = 1 in I) suggest significant distortion with internal angular increase at C_4, C_5 and decrease at C_3, C_6 in the direction of theoretical estimates. X-ray studies of related systems, e.g., benzo[1,2:4,5]dicyclobutene,[8] confirm more profound changes in structural parameters compared with an "ideal" or unstrained system.

One thorough analysis of the effects of strain in benzocycloalkenes on certain proton–proton spin coupling constants has been reported.[3b] Cooper and Manatt determined that strain exerted an ambivalent effect on $J_{1,2}$ ($^{3}J_{H,H}$) but $J_{1,3}$ ($^{4}J_{H,H}$) decreased and $J_{1,4}$ ($^{5}J_{H,H}$) increased substantially, and the effects of bond length, angle, and electronegativity changes were discussed. Using CNDO/2 minimized geometries,[9] impressive agreement in trends in the various $J_{H,H}$ was obtained, and indicated to the authors that the calculated geometries and charge densities by CNDO/2 were, in all likelihood, close to the truth.

In connection with an investigation of the ^{13}C NMR spectra of certain silicon analogues[10] of the benzocycloalkenes, the question of "ring-strain" effects on aryl-carbon chemical shifts arose, and we therefore commenced an examination of the spectra of the benzocycloalkenes themselves. This study seemed potentially illuminating since rather substantial variations in the aryl ^{13}C shifts were expected, and could be construed as a reflection of bond-order and charge density fluctuations at the nuclei directly in the ring. In any event, the data were of considerable importance, since they would need to be accommodated in some way by more refined theories of the ^{13}C chemical shift. Scattered pieces of data on one or two benzocycloalkenes did exist in an obscure fashion in the literature, but critical spectral assignments were not substantiated. It emerged that two other parallel investigations in the same area were being conducted and were reported,[11,12] but some of the assignments in one report[11] are now known to require modification. In our work, it became clear that strategically fluoro-substituted derivatives of the benzocycloalkenes were of much assistance in the vexing question of assignments in the hydrocarbons, but in addition afforded data of other interest. The necessity to synthesise certain deuterated derivatives stimulated a curiosity in previous suggestions[3b,13] of ^{1}H NMR assignments and our conclusions in this direction are also presented.

With the increasing appreciation of the insight available from ^{13}C relaxation measurements,[14] we have conducted such studies with some of the benzocycloalkenes, and the systematics of the results are rationalized in terms of differing contributions to relaxation from specific rotational modes.

Experimental Section

Compounds. *o*-Xylene, indan, and tetralin were commercial samples, and after distillation were of high purity as judged by vapor phase chromatography and ^{1}H NMR spectra. *o*-Di-*tert*-butylbenzene was kindly provided by Professor E. M. Arnett of the University of Pittsburgh. Benzocyclobutene was prepared as described by Oliver and Ongley.[15]

4-Deuteriobenzocyclobutene. Benzocyclobutene (10.4 g, 0.1 mol) was iodinated according to the procedure outlined for toluene

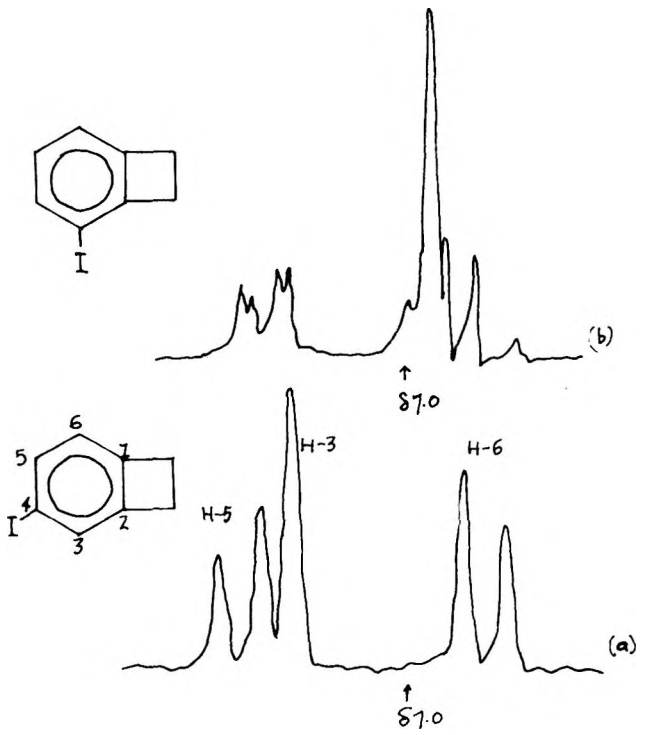


Figure 1. The aromatic portion of the 60-MHz ^{1}H NMR spectra of the separated 4-iodobenzocyclobutene (a) and 3-iodobenzocyclobutene (b) showing the characteristic pattern of the 1,2,4-proton substitution pattern in a.

by Wirth and co-workers.[16] Distillation of the crude product afforded three fractions: (a) unreacted benzocyclobutene (2 g); (b) a mixture of 3- and 4-iodobenzocyclobutenes (10 g, 56% yield based on consumed benzocyclobutene), bp 55 °C (0.01 Torr) [lit.[17] 55 °C (0.01 Torr)], n^{24}D 1.6393 (lit. 1.6395); (c) *o*-iodophenethyl acetate (1 g, 6%), bp 55 °C (0.01 Torr), n^{24}D 1.5784, ^{1}H NMR ($CDCl_3$) δ 1.98 (3 H, singlet, CH_3CO), 3.03 (2 H, triplet, J = 7 Hz, Ar-CH_2CH_2OAc), 4.23 (2 H, triplet, J = 7 Hz, $ArCH_2CH_2OAc$), and 7.0–7.82 (4 H, multiplet, Ar).

Fraction b was previously reported[17] to be pure 4-iodobenzocyclobutene. However, the ^{1}H NMR spectrum showed an impurity at δ 3.04 and a satisfactory integral ratio (4:3) was obtained only if the impurity signal was included in the calculation. This suggested the presence of an isomer. Combined gas chromatography–mass spectral analysis revealed two components in the ratio of 6.7:1, both exhibiting *m/e* 230 (M^+), and similar fragmentation patterns. The two components were separated on a 20 ft × 0.375 in. 30% SE-30 on Chromosorb W 45/60 column operating at 180°. The major component was shown to be the 4 isomer by conversion to the known[17] 4-carboxylic acid. The 4-iodo and 4-carboxyl compounds both displayed aryl ^{1}H NMR patterns requiring a 1,2,4 disposition of the protons.

The physical properties of the separated iodo isomers and the reported[17] mixture are as follows: (a) 3-iodobenzocyclobutene, bp 74 °C (0.9 Torr), n^{24}D 1.6333 (lit. 1.6335); (b) 4-iodobenzocyclobutene, bp 55 °C (0.1 Torr), n^{24}D 1.6403; (c) mixture, bp 55 °C (0.01 Torr), n^{24}D 1.6395. The aromatic regions of the ^{1}H NMR spectra are reproduced in Figure 1.

The Grignard reagent prepared from the mixture of iodobenzocyclobutenes was decomposed with D_2O (99.8%) and manipulated in the usual way to give a mixture of predominantly 4-deuteriobenzocyclobutene. The deuterium content was 67% by ^{1}H NMR and mass spectrometry.

5-Deuterioindan. Indan (100 g, 0.85 mol) was acetylated according to the method of Vaughan and co-workers.[18] Distillation of the crude product provided 5-acetylindan as a colorless oil (80.0 g, 60%), bp 80 °C (0.2 Torr) [lit.[18] 142 °C (15 Torr)], the constitution of which had been established by synthesis.[18,19] This is absolutely in agreement with the ^{1}H NMR spectrum (60 MHz, CCl_4, Me_4Si): δ 1.80–2.4 (unsymmetrical quintet, 2 H, J_{app} = 7 Hz, $-CH_2-CH_2CH_2-$), 2.45 (singlet, 3 H, $COCH_3$), 2.9 (unsymmetrical triplet, 4 H, J_{app} = 7 Hz, $-CH_2CH_2CH_2-$); the aryl portion consisted of an AB pattern centered at δ 7.2 and 7.65, J_{AB} = 8.5 Hz, with the low-field resonance of the δ 7.65 pattern underlying a "singlet" (δ 7.71, br, 1 H). This aryl pattern is consistent only with a 1,2,4 disposition of the protons.

The above ketone was transformed via its oxime and amine to 5-bromoindan, bp 64–65 °C (1 Torr) [lit.[20] 113 °C (14 Torr)], by well-documented procedures. The physical properties of the intermediates encountered in this conversion are as follows: 5-indanylmethylketooxime, mp 112–113 °C (lit.[21] 114 °C); 5-acetamidoindan, mp 106 °C (lit.[22] 107 °C); 5-aminoindan, mp 35–36 °C (lit.[23] 37–38 °C).

The Grignard reagent from the bromide was prepared (in THF) in the standard way and quenched with D_2O, to provide 5-deuterioindan, bp 64 °C (15 Torr). A 70% incorporation of deuterium was indicated by ^{1}H NMR and mass spectrometry.

4-Fluoro-*o*-xylene, 6-fluorotetralin, and 5-fluoroindan have been described previously,[24] as has 4-fluorobenzocyclobutene.[25] 3-Fluoro-*o*-xylene, 5-fluorotetralin, 4-fluoroindan, and 3-fluorobenzocyclobutene were available from another investigation, and will be described elsewhere.[26]

^{13}C Spectra. The spectra were obtained for $CDCl_3$ solutions (~25% solutions) and chemical shifts are referred to internal Me_4Si. In a few cases, cyclohexane was used as internal reference and the data connected to the Me_4Si scale by using $\delta_C = 27.5 + \delta_{C_6H_{12}}$. The spectra were recorded either at 15.086 MHz (CW) using a modified[27] HA-60 spectrometer, or a Bruker HX-90 using the PFT technique. J values are considered accurate to ±0.1 Hz on small couplings and ±1 Hz on the larger one-bond couplings. Chemical shifts are accurate to ±0.1 ppm.

^{13}C spin-lattice relaxation times were determined using the PRFT method[28] on solutions containing 5% C_6D_6 for internal lock. The 90° pulse time was set beforehand on a sample of C_6H_6 and was found to be 18 μs. A recycle time at least four times the longest T_1 to be determined was used in data acquisition. At least eight τ values in the (180–τ–90°) pulse sequence were used in determining any T_1 value. Narrow spectral widths were used to ensure sufficient data points to define the line shape and thus to yield accurate values of the peak intensities at different τ settings.

^{1}H Spectra. These were determined for CCl_4 or $CDCl_3$ solutions (5–10%) with internal Me_4Si, using a JEOL MH-100 spectrometer.

Results and Discussion

Assignments. General. A number of techniques and criteria are now available and applied in a routine fashion. For example, off-resonance noise decoupling[29] is successful for identifying quaternary carbons, which in addition generally occur at substantially lower field than protonated carbons. Off-resonance decoupling is similarly useful, but of course cannot distinguish between various =CH– aryl groupings, which is the chief assignment problem in the present work. Deuterium substitution,[30] when synthetically feasible, is unambiguous and has been employed in crucial aspects of this work, but other approaches are also useful, and particular mention of Gunther's so-called "fingerprint" method[31] is warranted. The bases for our assignments are presented below.

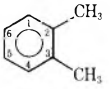
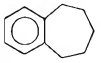
***o*-Xylene.** The spectrum has been assigned quite definitely by examination of both the 3-[10,11] and 4-deuterio[10] derivatives.

***o*-Di-*tert*-butylbenzene.** We utilized the technique (reported by Günther)[31a] that the splitting patterns observed for the ^{13}C signals in the ^{1}H-*coupled* spectra of symmetrically ortho-disubstituted benzenes differ characteristically for carbons α and β, i.e., $C_{3,6}$ and $C_{4,5}$, respectively, and give rise to "fingerprints".[31b] Examination of our 22.63-MHz spectrum revealed a close similarity in forms to Günther's calculated spectra[31] and those of other symmetric ortho-disubstituted benzenes for which C_α, C_β assignments had been established. Other workers[11] arrived at the same assignments by using the coherent ^{1}H decoupling method, assuming the correctness of the ^{1}H shifts (vide infra).

This approach (i.e., the "fingerprint" method) is also the basis for the assignments of entries 3 and 7 in Table I.

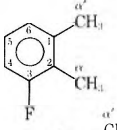
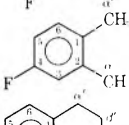
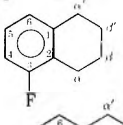
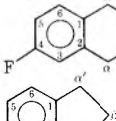
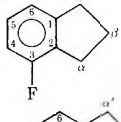
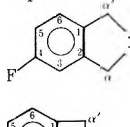
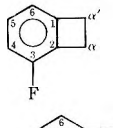
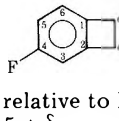
Tetralin. The assignments in Table I have been confirmed by specific deuteration, as well as the characteristic C_α, C_β "fingerprints" in the ^{1}H-coupled spectrum. It will be

Table I. Carbon-13 Assignments[a] of Benzocycloalkenes and 1,2-Dialkylbenzenes

Registry no.	Entry	Compd	Aromatic carbons 1	2	3	4	5	6	Aliphatic carbons α	β	γ
95-47-6	1		136.3	136.3	129.8	126.0	126.0	129.8	19.4		
	1[b]		136.21	136.21	129.84	126.11	126.11	129.84	19.44		
1012-76-6	2		148.4	148.4	129.4	125.6	125.6	129.4	37.75[b]	35.27[b]	
	3[c]		142.7	142.7	128.7	125.7	125.7	128.7	36.6	28.2	32.6
119-64-2	4		137.0	137.0	129.2	125.2	125.2	129.2	29.7	23.6	
496-11-7	5		144.0	144.0	124.4	126.2	126.2	124.4	33.8	25.4	
694-87-1	6		145.6	145.6	122.1	126.6	126.6	122.1	29.4		
	7[c]		125.4	125.4	114.7	128.8	128.8	114.7	18.4		

[a] Numbering system for convenience only. Chemical shifts relative to Me_4Si. More positive values correspond to lower shielding. With cyclohexane as internal reference, $\delta_C = 27.5 + \delta_{C_6H_{12}}$. [b] From ref 11. [c] From 12.

Table II. Carbon-13 Assignments[a,b] of Fluorobenzocycloalkenes and Fluoro-1,2-dialkylbenzenes

Registry no.	Entry	Compd	Aromatic carbons 1	2	3	4	5	6	Aliphatic carbons α	β	β′	α′
443-82-3	1		139.1	123.4	161.7	112.67	127.0	125.32	10.55			19.39
			(4.6)	(16.0)	(242.90)	(23.9)	(9.76)	(2.44)	(6.10)			(3.66)
452-64-2	2		131.6	138.2	115.9	161.5	111.9	130.4	13.9			18.0
			(2.5)	(7.2)	(21.2)	(244)	(20.3)	(7.4)	(1.5)			(n.o)
700-45-8	3		139.67	124.55	161.41	111.88	126.26	124.59	22.14	22.60	23.03	29.43
			(4.88)	(16.8)	(244.14)	(21.97)	(8.54)	(3.66)	(3.66)	(n.o)	(n.o)	(3.66)
2840-40-6	4		132.4	139.0	114.9	161.1	112.1	130.2	29.4	22.8	23.2	28.6
			(2.3)	(7.0)	(20.3)	(245.9)	(20.9)	(7.6)	(1.4)	(n.o)	(n.o)	(n.o)
57526-99-5	5		148.11	130.09	160.03	112.77	128.15	120.16	28.81	25.46		33.28
			(6.10)	(18.31)	(245.36)	(20.75)	(6.10)	(3.66)	(n.o)	(n.o)		(2.44)
37530-82-8	6		139.5	146.1	111.0	162.4	112.5	124.9	32.0	25.8		33.0
			(2.11)	(8.3)	(22.1)	(244.2)	(23.0)	(8.6)	(2.2)	(n.o)		(n.o)
51736-79-9	7		148.89	129.6	156.47	113.75	129.23	119.06	27.08			30.00
			(9.76)	(15.6)	(255.1)	(20.75)	(6.10)	(4.89)	(n.o)			(2.44)
51736-78-8	8		140.5	146.6	110.0	163.1	113.8	123.7	28.6			28.5
			(2.0)	(7.5)	(22.2)	(245.3)	(23.6)	(8.2)	(2.0)			(n.o)

[a] Chemical shifts relative to Me_4Si. More positive values correspond to lower shielding. With cyclohexane as internal reference, $\delta_C = 27.5 + \delta_{C_6H_{12}}$ [b] Values in parentheses are $^{13}C-^{19}F$ couplings. Numbering system for convenience only.

instructive to consider how the data for the fluorotetralins (entries 3 and 4 in Table II) can be scrutinized to reveal the correct assignments for tetralin itself (vide infra).

Indan. The aromatic carbons were distinguished by examination of 5-deuterioindan (D at position 4 in entry 5, Table I) which was synthesized from authentic 5-acetylindan by an unambiguous sequence. (See Experimental Section.)

The same order of aryl carbon shifts has been obtained by Günther.[12] Previously we had correctly deduced[10] these assignments from examination of the fluoroindans. Incorrect assignments have been reported,[11] based on the coherent ^1H decoupling technique, which is somewhat surprising as the ^1H chemical shifts[3b] utilized in this work have since been demonstrated to be correct (vide infra). Buchanan and Wightman,[32a] in a quite separate study, did correctly

tabulate the shifts for indan, but these were unproven.[32b] Some time ago, the comparative data for indan and 1,3-dimethylindan were available,[10,33] but generally overlooked, and consideration of the γ effect (shielding) of the CH_3 group at C_α leads directly to the assignments given.

Benzocyclobutene. Deuterium introduction into benzocyclobutene was achieved via the iodo compound using standard organic transformation. Examination of a system with predominant D location at C_β confirmed the assignments in Table I. Another approach has given identical assignments.[12]

Maciel and co-workers reported[11] reversed assignments for $C_{3,6}$, $C_{4,5}$ but their coherent decoupling technique was based on an assumed correctness of the previously suggested order of the ^1H chemical shifts. Our examination of the deuterated benzocyclobutene and ^{13}C satellite studies shows that the previous suggested order of ^1H shifts[3b] need reversal, and ipso facto any soundly determined ^{13}C assignments based on these ^1H shifts. The correct set of assignments have also been reported by Jones, Garratt, and Vollhardt,[34] in another connection, apparently on the basis of differential Overhauser effects.

Benzocyclopropene. These data are based on the "fingerprint" criterion of Günther for C_α, C_β resonances.[12]

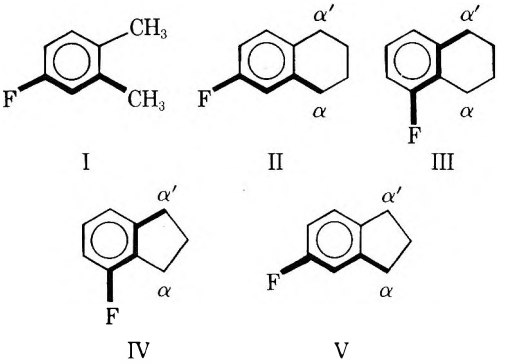
Benzosuberane. The spectrum was similarly assigned[12] and the correct assignments were suggested by Maciel,[11] on the basis presumably that the more remote $C_{4,5}$ should resemble $C_{4,5}$ in a relatively "strain-free" *o*-dialkylbenzene.

With the various approaches that have been applied to the problem of distinguishing $C_{3,6}$ (C_α) and $C_{4,5}$ (C_β) in entries 1–7 (Table I), there is no doubt that the listed aromatic assignments are correct. Regarding aliphatic carbon assignments (entries 2–5, Table I) no difference of opinion exists and considerations of one or a combination of off-resonance decoupling, selective deuteration, chemical shifts, and relative intensities, etc., yield concordant conclusions.[1,10,11,12]

^{13}C Assignments in Fluorobenzocycloalkenes (Table II). Aryl Carbons. Under conditions of broad-band proton decoupling, all aromatic carbons in Table II appear as doublets due to ^{13}C–^{19}F coupling. This apparent spectral complexity is a blessing since it has been established quite clearly that in phenyl systems this coupling declines in a regular way with the number of intervening bonds.[1,10,35] One-bond couplings usually are in the range 240–250 Hz, while coupling to secondary ortho carbons (i.e., $^2J_{C-F}$) are 20–24 Hz. A *reduced* ortho ($^2J_{C-F}$) coupling to tertiary carbons is observed (ca. 15–18 Hz), but substantially larger than coupling ($^3J_{C-F}$) to tertiary meta carbons, typical values being in the range 4–9 Hz. Coupling to secondary meta carbons is generally somewhat larger (6–10 Hz), but this similarity in values never poses a problem since the chemical shifts are quite different. Easily resolved coupling to para carbons is also observed ($^4J_{C-F}$) ranging from 2 to 4 Hz. Intensity variations are pronounced as well, and the signals of the much less intense nonprotonated carbons are assigned without difficulty. An added benefit of fluorine substitution is the pronounced effect on the chemical shift. Carbon bearing fluorine, besides having a large one-bond coupling diagnostic in itself, is quite deshielded (by ~32 ppm) whereas carbons ortho to fluorine are shifted upfield by 13–14 ppm. Carbons para to fluorine are also shielded by a lesser amount (~4–5 ppm) whereas meta carbons appear always to be deshielded by about 1–2 ppm. Considerations of these data lead generally to a unique assignment for a fluorophenyl system.[1,10,35]

Consider the assignments for the fluorotetralin (entry 3) in Table II. Six doublets at 161.41 ppm (J_{C-F} = 244.1 Hz), 139.67 (4.88), 126.2 (8.54), 124.59 (3.66), 124.55 (16.8), and 111.88 (21.97) are observed in the aromatic region. C_3 (bearing fluorine) corresponds to 161.41 (244.14) on the basis of chemical shift and coupling, and C_4 to 11.888 (21.97) since this coupling is typical of $^2J_{C-F}$ to a secondary carbon. A coupling of 16.8 Hz is too large to be $^3J_{C-F}$ but is appropriate for $^2J_{C-F}$ to a quaternary carbon. C_2 is therefore identified and confirmed by intensity considerations. The 8.54-Hz coupling is appropriate for $^3J_{C-F}$ (secondary) and locates C_5. The remaining resonances 139.67 (4.88) and 124.59 (3.66) are straightforwardly allocated to C_1 and C_6 on the basis of chemical shift and coupling constants. With these assignments for entry 3, and considering the substituent effects of fluorine in phenyl systems (vide supra), we can calculate the following aromatic shifts (parts per million) for tetralin itself: C_1, 138.17; C_2, 138.00; C_3, 129.41; C_4, 125.4; C_5, 124.76; C_6, 129.09. [In tetralin the carbon pairs are (C_1, C_2), (C_3, C_6), and (C_4, C_5)]. The agreement between these and those rigorously assigned demonstrates how regular ^{19}F contributions to carbon screenings are. Although some variations must occur depending on the particular phenyl system,[36] these seem to be minor and it is clear that these well-behaved effects of ^{19}F substitution are extremely useful for assignment purposes in the parent hydrocarbon, particularly when there is 3–4 ppm difference in shifts of contentious resonances. This can be confirmed by examining appropriate sets of other data in Tables I and II. Strategic D substitution[30] is in principle a better tactic since very minor perturbation of the system results. While carbon bearing deuterium is hence readily assigned, some care is required if adjacent carbons are to be assigned by isotope shifts, signal broadening (^{13}C–D coupling), etc., and a satisfactorily high D incorporation is required. Since fluorine can be introduced easily into aryl systems by manipulation of readily installed functionality, its use in the presently described connection is worthy of note.

Aliphatic Carbons. Chemical shifts and ^{13}C–^{19}F couplings lead to acceptable assignments in all cases, except the β,β' carbons in entries 3 and 4: for 3-fluoro-o-xylene (entry 1) resonances at 19.39 (3.66) and 10.55 ppm (6.10) are observed compared with 19.4 ppm for the methyl carbon in *o*-xylene. As the methyl ortho to fluorine should experience substantial shielding, the indicated assignments are arrived at. These data provide values of $^4J_{C-F}$ and $^3J_{C-F}$ of 3.66 and 6.10 Hz, respectively. In the fluorobenzocycloalkenes this latter value (i.e., $^3J_{C-F}$) depends strongly on the fused ring, and may be vanishingly small. In 4-fluoro-*o*-xylene (entry 2, Table II) the CH_3 signals are less separated and one has significant coupling (1.5 Hz). Two lines of reasoning provide the indicated assignments. α CH_3 is attached to a more electronegative aryl carbon (meta to fluorine) than is α' CH_3 (para to fluorine) and the 1.5-Hz coupling is consistent with a preferred "zigzag" array of coupled atoms and shorter internuclear path (I). In



agreement with this, Weigert and Roberts[35] observed fluorine coupling to the methyl carbon in *m*-fluorotoluene, but

not in *p*-fluorotoluene. Similar ^{13}C–^{19}F couplings across a "zigzag" path have been observed in other fluoroaliphatic compounds,[37] and the suggestion has been made that such ^{13}C–^{19}F scalar coupling is transmitted by a "back orbital" lobe on the fluorine interacting directly with the carbon orbital. Such an interaction is favored by a "zigzag" array of the coupled nuclei. The validity of this suggestion is clear from the fluorotetralin data (entry 4) where coupling to C_α but not to $C_{\alpha'}$ is observed (II). In entry 3, C_α, $C_{\alpha'}$ are distinguished by their large chemical shift difference, but again "zigzag" coupling over four bonds is similar to a less preferred geometry spanning three bonds (III). $\delta_{C_\beta,C_{\beta'}}$ in entries 3 and 4 are very similar and are not distinguished. Regarding the fluoroindans (entries 5 and 6) C_β is assigned on the basis of its similar chemical shifts (25.46, 25.8 ppm) to C_β in indan (25.4 ppm) and the lack of ^{19}F coupling. In entry 5, $C_{\alpha'}$, $C_{\alpha'}$ are allocated unambiguously on the basis of chemical shifts (C_α shielded by 5 ppm, $C_{\alpha'}$ similar to C_α in indan) and again coupling is observed to $C_{\alpha'}$ (2.44 Hz) (IV) with the favorable geometric array, but not to C_α, with one less intervening bond. In entry 6, C_α and $C_{\alpha'}$ are separated on the basis of the preferred coupling to C_α (V). Similar strategies apply to the fluorobenzocyclobutenes where zigzag coupling $^4J_{C'}$ (2.44 Hz) is observed but ^3J_C is not (entry 7) and in entry 8, α C is seen to have the requisite geometry with respect to fluorine for coupling. These geometrical dependences of $^3J_{C-F}$ and $^4J_{C-F}$ seem to have sufficient generality as to be useful considerations for assignment in fluoroarylalkyl systems.

Benzocycloalkenes. Chemical Shift Trends. Aromatic Carbons. It is useful to determine whether any trends emerge in these shifts with geometrical factors, and what relation these trends may have with available theoretical parameters and explanations of "ring strain". A previous analysis of some of these shifts which indicated somewhat irregular response to strain is no longer relevant because of misassignment of key signals. Scrutiny of the data in Table I reveals the following.

$C_{1,2}$. These carbon shifts span a range of some 23 ppm (148.4 ppm for o-di-*tert*-butylbenzene to 125.4 ppm for benzocyclopropene) but a smooth trend is not exhibited as the size of the fused ring alters. Dissection of the shift change into a "strain" component is very difficult since α, β, γ screening effects differ with ring size. Nevertheless, with decreasing ring size and therefore more planar structures, and also less effective and essentially constant β effects, the sequence 137.0 (tetralin), 144.0 (indan), 145.6 (benzocyclobutene), and 125.1 (benzocyclopropene) must be substantially a manifestation of bond order, change density, and hybridization effects, rather than steric effects from the alkyl ring. Increased strain then seems to be associated with a deshielding effect at $C_{1,2}$ except for benzocyclopropene. However, in this case, $C_{1,2}$ is part of the cyclopropane ring system, and it is established that cyclopropyl carbons experience substantial shielding. Therefore a major contribution to the shielding of $C_{1,2}$ in this case must be associated with the special nature of this ring system.

$C_{3,6}$ (C_α) and $C_{4,5}$ (C_β). A clearer picture emerges here since the increasing strain is associated with increased shielding, from ca. 129 ppm for "strain-free" cases (entries 1–4, Table I) to 114.7 ppm in a regular fashion. Reduced effects operate at $C_{4,5}$ but a slight (~3 ppm) decrease in shielding occurs. Clearly $C_{4,5}$ is not very sensitive at all to ring-size effects and this is consistent with very similar reactivities at β positions in benzocycloalkenes in conventional electrophilic substitutions.[38] As rate measurements reflect details of the transition state, more meaningful comparisons may be made with ^{19}F shieldings, known to be highly sensitive to (ground-state) electron density fluctuations in aromatic systems. Relative to fluorobenzene, the ^{19}F chemical shifts of 4-fluoro-*o*-xylene, 6-fluorotetralin, and 5-fluoroindan are very similar, +5.57, +5.45, and 5.23 ppm, respectively[25] (+ indicates to higher field in ^{19}F shielding convention). Similar trends emerge in the fluorobenzocycloalkenes and attention is best focussed on entries 2, 4, 6, and 8 in Table II, i.e., the 4-fluoro series, since some nonbonded effects between fluorine and the adjacent methylene in the 3 series could occur conceivably. C_1 in this series ranges from 131.6 to 140.5 ppm, C_6 from 130.4 to 123.7 ppm, and C_5 from 111.9 to 113.8 ppm. Assuming fluorine contributions to screenings to be essentially constant, these trends are very similar to these for the hydrocarbons.

The relation between π-electron density and carbon-13 chemical shifts has been explored for some time and an early LCAO analysis concluded that there was a local charge dependence agreeing in sign and order of magnitude with experiment.[39] In substituted benzenes, for example, para-carbon shifts correlate well with other measures of substituent effects and with calculated (CNDO/2) total and π-charge density.[40] In these cases apparently other terms change in proportion with charge density, or in a minor way, so overall correlation is observed. That the situation is more complex for polycyclic aryl systems was revealed by the work of Alger, Grant, and Paul,[41] who considered other effects in their treatment. A general expression of the form

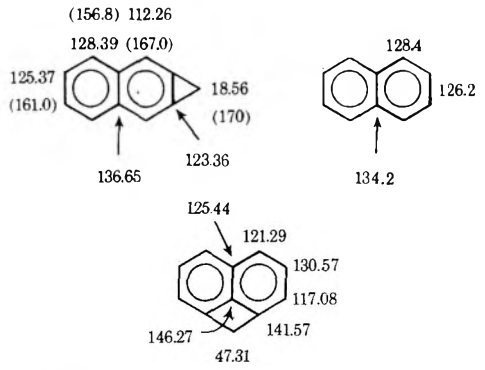
$$\delta_{13C} = \frac{1}{\Delta E}(A\pi\Delta Q\pi + B_\sigma\Delta Q_\sigma - C_p\Delta P)$$

where $\Delta Q\pi$, ΔQ_σ, and ΔP are the π charge, σ charge, and total mobile bond order relative to the benzene values, was developed and applied to some alternate aromatic molecules.

In the present cases of the benzocycloalkenes, contributions from both charge densities and bond-order changes with ring size presumably occur. Fortunately, careful scrutiny of the data for the tetralin and indan systems provides the key to a meaningful analysis of the problem. Compared with fluorobenzene, ^{19}F shieldings of +5.03, +6.12, and +5.42 ppm are observed[26] for 3-fluoro-*o*-xylene, 5-fluorotetralin, and 4-fluoroindan, respectively, indicating modest charge density and C–F π-bond order differences at C_α for the tetralin–indan duo. The values of $J_{^{13}C_\alpha-H}$ for the pair are also essentially identical.[12] In impressive contrast, the less sensitive $^{13}C_\alpha$ probe registers a −4.8 ppm difference (i.e., to higher field) for the same pair (Table I). These results seem to demand that some factor very modestly (if at all) affecting the ^{19}F shifts is having a substantial effect on the related $^{13}C_\alpha$ shifts. The direction of this effect is to higher field, opposite to that expected on the basis of diminished charge density at C_α.[40] We therefore conclude that the ΔP term above must exercise a decisive influence on the resultant C_α shieldings and it is possible to extrapolate in a qualitative way from the proposal of Streitweiser[5] regarding these systems. As the "ring strain" increases the decreasing angles about carbon in the fused ring are associated with higher "p character" in these carbon orbitals, and hence the orbitals directed toward C_α have higher "s character". This increase in orbital electronegativity causes a polarization of electrons away from C_α which becomes more electronegative. This ground-state change accounts for $J_{C_\alpha-^1H} > J_{C_\beta-^1H}$ in benzocyclobutene[12] and increased acidity at the α positions.[5,6] As pointed out above, it does not rationalize the shift trends if charge density alone is invoked. However, there must also be changes in p-bond orders about C_α and the bridgehead carbons, and as strain increases, this term must increase between bridgehead carbons, but decrease between these carbons and C_α. This

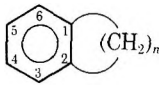
would suggest decreased shielding for bridgehead carbons, but increased shielding for C_α.

"Strain" has significant effects on ^{13}C shifts in naphtho systems also. Naphtho[*b*]cyclopropene has been examined and the fully proton-coupled spectrum[12] provides the assignments shown below. (Values in parentheses are $^1J_{C-H}$.)



On comparison with naphthalene, fusion of the strained ring has consequences very similar to those observed in the benzocyclopropene case. C_α experiences substantial shielding (−16.14 ppm) while C_β (now the quaternary carbon) is deshielded (+2.45 ppm). The assignments recently listed for 1,8-methanonaphthalene (1*H*-cyclobuta[*de*]-naphthalene) have been reproduced above, and confirm 1,8 bridging to have serious effects also.

Quantitative assessment of the situation in terms of the theory is difficult for several reasons. Firstly, as described by Alger, Paul, and Grant,[41] and polarization and bond-order coefficients A_π, B_δ, etc., are functions of the assumed overlap integrals, and the character of the wave functions chosen. Secondly, accurate structural data for the lower members of the benzocycloalkenes are lacking, as are refined MO calculations for these molecules. However, Cheung, Cooper, and Manatt[9] have applied the CNDO/2 semiempirical method to these cases, and it is of interest to summarize their findings. Regarding bond orders, both the C_{2s} and $C_{2p\pi}$ components to the C_5–C_6 bond decrease, yielding a substantial decrease in bond order while the C_{2s} component to the C_1–C_6 bond increases but also does the $C_{2p\pi}$ component.



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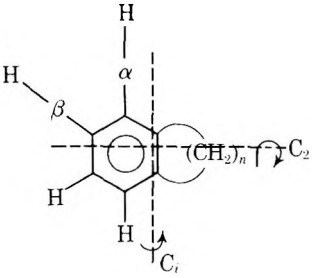
This latter result is surprising in view of the p-orbital reorganization toward the fused ring. The effect of increasing strain is to increase total electron density at C_5 and C_6 (largely because of changes in $2p\pi$ density with irregular C_{2s} contributions) while at C_1, total charge density decreases with strain, as does the C_{2s} component, but the $C_{2p\pi}$ portion fluctuates. While there are some encouraging aspects in these result, and some accord with experimental findings, it is necessary to point out that others considered the CNDO/2 approach somewhat crude, with drastic and unreal assumptions, to contribute anything meaningful to the interpretation of strain in these molecules. This is because the semiempirical methods (CNDO, INDO, MINDO) are parameterized with respect to nonstrained systems, but Streitweiser recently established[43] that ab initio methods confirm the earlier qualitative proposal that compression of bond angles results in enhanced acidity of adjacent C–H bonds. Accurate molecular geometries are required for n = 1, 2 to allow more refined theoretical treatment of these molecules. However, the ^{13}C data reported herein do confirm that special care is required in interpreting such shifts in cases where bridgehead carbons and substantial bond-order fluctuations occur, and the simple correlations with π or total charge may break down.

^{13}C–^{19}F Couplings. Most features of the spectra of the fluorobenzocycloalkenes have been outlined but there are trends in ^{13}C–^{19}F couplings with ring size that are worthy of note. In the 4-fluoro derivatives (entries 2, 4, 6, and 8, Table II) the one-bond J_{C-F} are 245 ± 1 Hz, suggesting rather minor variations in C–F bond character and effective nuclear charge. However, in the 3-fluoro derivatives, a wider range is encountered from 244.0 Hz (entry 3, Table II) to 255.1 Hz for the benzocyclobutene (entry 7, Table II). One other aromatic J_{C-F} in excess of 255 Hz (255.3 Hz) has been reported[44] (for 1,8-difluoronaphthalene) and steric effects were regarded as the likely cause of the exalted value. In the present case, the steric environment of the 3-fluorine does not seem congested enough to explain completely this large exaltation, and the altered s character and effective nuclear charge at C_α is probably largely responsible.[45] Some other variations with ring size in $^nJ_{C-F}$ in the aryl ring are also evident but in view of the poor understanding of factors responsible for $^{n>1}J_{C-F}$, discussion of these trends is not pursued here, although possible factors are outlined elsewhere.[46]

Relaxation (T_1) Measurements. As a further possible aid to the ^{13}C chemical shift assignments and in order to investigate the microdynamics of this type of molecule in solution we have measured the ^{13}C T_1 values of the protonated carbons. (We have excluded from discussion the T_1 values of the methyl carbons because of the additional effect of internal motion.[47]) There is convincing evidence from previous studies[48] that the relaxation mechanism of protonated carbons in compounds of this type will be dominated by the ^{13}C–^1H dipolar interactions. We assume this to be so in the following discussion.

Inspection of the results in Table III shows that for the benzocycloalkenes and *o*-xylene, the T_1 of C_α is always *longer* than that of C_β. We ascribe this behavior to anisotropic rotational reorientation of the molecule. Although the theoretical description of the situation is often difficult to treat quantitatively, that such a result is reasonable can be appreciated in a qualitative way from inspection of models of these compounds and consideration of the relative magnitudes of the reorientation rates about the various principal axes.



We have depicted above what we believe is a reasonable approximation to the principal reorientation axes of the molecules. Not drawn is the rotation axis perpendicular to the plane of the molecule. Grant[49] has applied Woessner's treatment of an ellipsoidal tumbler to analyze motion in some near-ellipsoidal molecules such as *trans*-decalin and has demonstrated a good correlation between the ellipticity about a rotation axis and the reorientation rate about the same axis and this treatment predicts $R_2 > R_i$, where R_2 and R_i are the reorientation rates about the appropriate axes shown above. (An alternative approach would involve consideration of relative moments of inertia about C_2 and C_i axes.) The effect these rates have on the various ^{13}C T_1

Table III. Carbon-13 Spin-Lattice Relaxation Times[a] for the Protonated Carbons of *o*-Xylene and Benzocycloalkenes

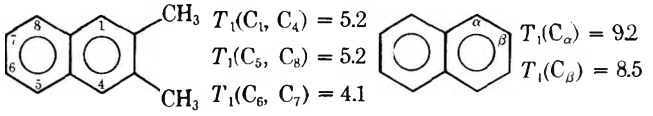
Compd	T_1, s			
	Ar–C_α	Ar–C_β	α-CH_2	β-CH_2
o-Xylene	10.8	8.9		
Tetralin	7.1	5.7	3.7	3.6
Indan	10.1	8.0	5.3	6.4
Benzocyclobutene	10.5	8.9		

[a] Determined using PRFT method as per Experimental Section.

values depends on the angle the C–H vector makes with these axes. If the angle is zero (as is the case of the C_α–H vector and C_i axis) then motion about this axis will not contribute to the relaxation as no change in the C–H vector occurs. As an approximation, the larger the angle the more influence reorientation about the axis has on T_1.

Consider motion about the C_2 axis: the C_α–H vector makes an angle of 90° while the C_β–H vector makes an angle of 30°. Thus, fast motion about the C_2 axis will have a larger influence on the C_α T_1 than on the C_β T_1. As a consequence, the T_1 of C_α will be longer given the inverse relation between T_1 and the correlation time. A similar result has been observed[50] in substituted biphenyls where the para carbon has the shortest T_1, internal motion of the phenyl groups not having any influence on the relaxation processes of this carbon.

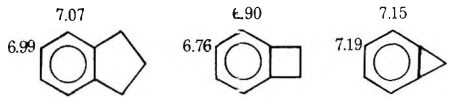
The effect described above is operative in other compounds with the appropriate symmetry level and this technique, if applied correctly, may be generally useful for spectral assignments, e.g.



The pattern of the T_1 values (Table III) for the protonated aromatic carbons is in accord with rigorously established assignments presented in this paper, and those in the literature for naphthalene[41] and 2,3-dimethylnaphthalene.[52]

The variation of the T_1 values between the aromatic and aliphatic carbons is interesting. They are not related simply to the number of attached protons, the aliphatic carbon T_1's being somewhat longer than expected. There is no difference in the T_1's for these carbons in tetralin (nonplanar fused ring) and only a slight variation for indan (planar fused ring). It appears that anisotropic reorientation has less of an influence on the relaxation processes of these carbons.

^1H Chemical Shifts. The necessity to synthesize certain deuterium-labeled benzocycloalkenes prompted examination of their ^1H NMR spectra, since it seemed that positive conclusions would result. Previously Mannatt and Cooper,[3b] in their thorough study of ^1H–^1H coupling in these molecules, had analyzed the AA′BB′ system of the aromatic protons, but δ_A and δ_B are not explicit from such an analysis. It was suggested that the broadened half of the AA′BB′ pattern corresponded to H_α, on the basis of preferred coupling (over H_β) to the methylene protons. In this way, suggested assignments for indan, benzocyclobutene, and benzocyclopropene were presented, and shown below (δ from Me_4Si).

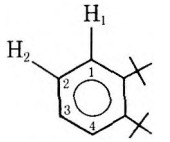


Subsequently, Maciel[11] was guided by these assignments in his approach to the corresponding ^{13}C assignments, which were contrary to ours and Günther's[12] for n = 1, 2, 3. It was therefore a matter of interest whether the ^1H assignments were in error, and therefore the major cause of the discrepancies in the ^{13}C data. It should be made clear that the main thrust of Mannatt and Cooper's work concerned the variation of ^1H–^1H couplings with structural factors, and the order of ^1H assignments was not necessary for any of their conclusions.

We have utilized two approaches to distinguish H_α, H_β in the ^1H spectra of indan and benzocyclobutene. The first is unambiguous, and involves careful examination and integration of the tactically deuterated analogue. 5-Deuterioindan (~70% D) was examined and it was quite clear that the higher field part of the AA′BB′ system (270 Hz sweep width at 100 MHz) had suffered an intensity loss. The same system has also been examined by Günther,[52] with concordant conclusions. The assignments suggested by Mannatt and Cooper[3b] for indan are therefore established. At the time that we were examining approaches for assignment of ^1H and ^{13}C frequencies in some AA′BB′ spectra, Günther kindly disclosed[53] a very useful technique, which is based on observation of the ^{13}C satellite pattern. The overall width must be larger for β protons than α protons, as $(2J_o + J_m) > (J_o + J_m + J_p)$. We applied this technique to the ^{13}C satellites of indan, but the very similar values of $J_{^{13}C-H_\alpha}$ and $J_{^{13}C-H_\beta}$ and small δ_α–δ_β resulted in some overlapping. Nevertheless, the higher field portion of the complete low-field satellite pattern was more spacious, corresponding to H_β at higher field, as already rigorously established.

Deuteriobenzocyclobutene was synthesized from a mixture of 4-iodo- (87%) and 3-iodobenzocyclobutene (13%) (as indicated in the Experimental Section) resulting in overall 67% D incorporation (mass spectrum). The relative intensities of H_α:H_β signals in the ^1H spectrum should be ca. 1.25–1.30. Scrutiny of the spectral trace (540 Hz sweep width, 100 MHz) (Figure 2a,b) shows quite definitely the lower field portion to be of reduced intensity, and several integrations confirm this ($H_\alpha/H_\beta \sim 1.35$). H_β is therefore at lower field, contrary to the previous suggestion. The high- and low-field ^{13}C satellite patterns for benzocyclobutene are relatively easy to identify, and it is quite clear (Figure 2c,d) that the more spacious patterns are associated with the lower field resonance, i.e., H_β at lower field, in agreement with the conclusion above.

o-Di-*tert*-butylbenzene was of particular interest, since although both reported assignments[1,11] of the ^{13}C spectrum were in agreement (vide supra), that of Maciel[11] was based on the application of coherent ^1H decoupling to the reported (now shown to be incorrect) aryl ^1H assignments. Castellano and Kostelnik[13] in a study of the various ^1H–^1H couplings in substituted benzenes, analyzed the AA′BB′ pattern of o-di-*tert*-butylbenzene, and reported without comment the following shifts.



δ_1 = 418.55 Hz = 6.97 ppm
δ_2 = 446.8 Hz = 7.44 ppm (Me_4Si)
Δ = 28.45 Hz (60 MHz)

Molecular models indicate substantial steric (nonbonded) interactions between the $-C(CH_3)_3$ group and H_1, and in the light of present knowledge, "steric deshielding"[54] would be consistent with a reversed order of these chemical shifts. This also yields a chemical shift for H_2 (6.97 ppm) almost identical with that for H_2 in tetralin (6.99 ppm).

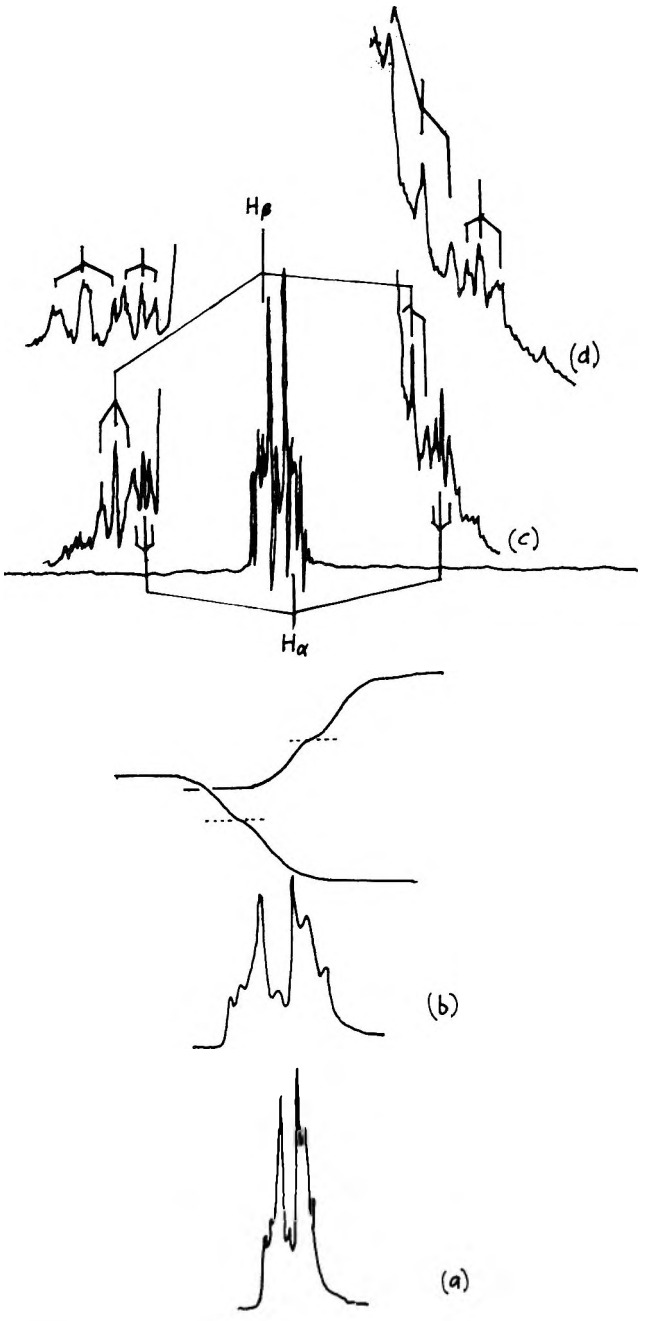


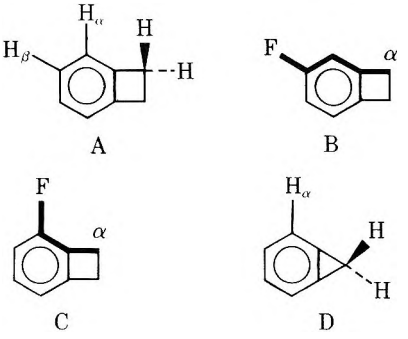
Figure 2. The aromatic portion of the 100-MHz ^1H NMR spectrum of benzocyclobutene selectively deuterium enriched at the 4 position on 1080-Hz sweep width (a) and 540-Hz sweep width (b). Integral traces for b are shown. (c) High-gain spectrum (1080-Hz sweep width) showing ^{13}C satellite patterns about H_α (higher field) and H_β. (d) As in c but 540-Hz sweep width.

This is expected, since H_2 is remote from the region of steric congestion.

Our proton-*coupled* ^{13}C spectrum of o-di-*tert*-butylbenzene, in addition to settling the C_β, C_β assignments (vide supra), provides values of $J_{^{13}C-H_1}$ = 154.8 and $J_{^{13}C-H_2}$ = 160.5 Hz (see numbering above). The difference in these coupling constants (5.7 Hz) is small in comparison with the chemical shift difference between H_1 and H_2 at 100 MHz (47.4 Hz), confirming that no "crossover" of the ^{13}C satellite patterns could occur. From the data of Kostelnik and Castellano,[13] it can be shown that the ^{13}C satellites about H_1 should have a total spacing of ca. 9–10 Hz, while those about H_2 should be ca. 16–17 Hz wide. In the 100-MHz ^1H spectrum of *o*-di-*tert*-butylbenzene, the low-field satellites about H_1 and H_2 were identified, and were separated by ca. 45.5 Hz [calculated 47.4 − ½(160.5 − 154.8) = 44.6 Hz]. (Slight impurities to the high-field side of the main aryl ^1H spectrum prevented identification of the high-field satellites.) The lowest field satellite pattern had a "spread" of ca. 10 Hz while the higher field one had a total spacing of ca. 16 Hz, demanding that H_1 be at lower field than H_2, as deduced from the chemical shift difference above. The suggestion of Kostelnik and Castellano[13] therefore requires reversal.

The spectrum of *o*-bis(trimethylsilyl)benzene also exhibits[55] a substantial chemical shift difference (ca. 0.4 ppm) for the sets of aromatic protons. Although no analysis was reported, chemical shifts of ca. δ 7.1 and 7.5 appear to apply, and it would seem that protons ortho to $Si(CH_3)_3$ are also sterically deshielded in this system, as expected. No studies of the ^{13}C satellite spectra were reported.

There are two aspects relating to the orders of ^1H and ^{13}C shifts now established in this series of molecules. Firstly, the ^{13}C shifts faithfully reflect the ^1H shifts within a molecule, and this type of correlation in substituted benzenes has been noted widely, particularly for para-carbon shifts.[40,56–58] In the present cases, a lack of correlation at the α position would not have been surprising, in view of the possible additional perturbations that might operate in this vicinity. Secondly, the ^1H assignments now established for benzocyclobutene indicate that the preferential broadening of one-half of the AA′BB′ aromatic pattern (the criterion used by Manatt and Cooper[3b] in their suggested H_α, H_β assignments) must involve H_β and the methylene protons, where a preferable geometry presumably exists. This is reminiscent of the situation in the fluorobenzocyclobutenes B and C, where observable $^4J_{C_\alpha-F}$ is observed (B, 2.0



Hz), but not $^3J_{C_\alpha-F}$ (C). While many factors affecting longer range proton–proton and carbon–fluorine coupling are undoubtedly different,[46] the geometry of the coupled nuclei is clearly of importance.

The situation for benzocyclopropene is unclear, as the aryl ^1H assignments have not been established, e.g., by selective deuteration. It would not be surprising, however, if H_α was more strongly coupled to the methylene protons than H_β since the geometry is now different (D) from the benzocyclobutene case.[59] Special electronic effects associated with the cyclopropyl ring may also be important.

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Registry No.—*o*-Iodophenethyl acetate, 57527-00-1; 3-iodobenzocyclobutene, 38122-16-6; 4-iodobenzocyclobutene, 1004-07-5; 5-acitylindan, 4228-10-8.

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The Substituent Effect of the Bromomethyl Group. A Carbon-13 Magnetic Resonance Study

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The natural abundance carbon-13 NMR spectra of benzyl bromide, 1- and 2-bromomethylnaphthalenes, 6-methyl-2-bromomethylnaphthalene, 4-bromomethylbiphenyl, and 9-bromomethylanthracene have been obtained and assigned. At each carbon position chemical shift differences ($\Delta\delta$) for the structural change $ArCH_3 \rightarrow ArCH_2Br$ have been tabulated, and for formally conjugated positions significant downfield shifts occur. The magnitudes of $\Delta\delta$ are very dependent on the aryl group and disposition, and correlate with theoretical measures of the *change* in π-charge density for $ArCH_3 \rightarrow ArCH_2^+$. This deshielding is considered to be associated with removal of π charge by C–Br hyperconjugative electron withdrawal, and parallels trends previously established by ^{19}F NMR measurements. This removal of π charge is not inconsistent with predominant (ortho, para) electrophilic substitution in benzyl halides if in the transition state rotation in $-CH_2X$ occurs to promote C–H hyperconjugative electron release, but necessarily impeding C–Br electron withdrawal.

The substituent effects of halogenated methyl groups are of much current interest, and a variety of approaches have been employed to assess them. Regarding electrophilic aromatic substitution, Ridd and co-workers[2] established that the $-CH_2Cl$ group had a definite ortho–para directing effect in nitration, and very recently Symons[3] regarded this as evidence for electron release *from* the carbon–halogen bond

$$-\overset{\delta+}{C}H_2-\overset{\delta-}{X}$$

despite the indicated polarization. The greater acidifying effect of $-CH_2X$ when para compared with meta on benzoic acid has been attributed by Exner to a π-inductive mechanism.[4] Studies[5] of electron-density distributions (in the ground state) in bromomethylaromatics by ^{19}F chemical shifts, and related computational work,[5,6] have indicated quite strongly that such groups are hyperconjugatively electron withdrawing, involving interaction of aryl-ring MO's with the polarized

$$\overset{\delta+\ \delta-}{C-X}$$

σ-bonding MO. Additional ^{19}F SCS[7a] data have been provided for a wide range of bicyclic systems, incorporating the benzylic C–X fragment[7b] (where X is appreciably more electronegative than carbon) in such a manner that C–X hyperconjugation was essentially impossible. As monitored by ^{19}F SCS, electron withdrawal was substantially reduced, but residual polar components still operated. Some earlier NQR (chlorine) results[8] were in line with the above conclusions.

In closely related series of aromatic compounds, ^{13}C chemical shifts have provided important insight into π-electron distributions, and such shifts correlate well with other measures of substituent–substrate interactions.[9–12] While in some respects complementing ^{19}F SCS, ^{13}C SCS provides simultaneous measures of perturbations at all carbons in the system, and provided care is exercised, therefore unveils a more detailed canvas. In view of our disinclination[7] to accept the proposal of Symons[3] regarding the mode of behavior of $-CH_2X$ (X = halogen), we deemed it essential to provide another measure of this substituent effect and to attempt to correlate the results with an established quantum mechanical description.

Experimental Section

Compounds. Toluene, 1- and 2-methylnaphthalenes, 2,6-dimethylnaphthalene, 4-methylbiphenyl, and 9-methylanthracene were commercially available, and samples utilized were of high purity as judged by vapor phase chromatography and ^1H and ^{13}C NMR spectra.

o-Deuteriotoluene was obtained by treating the Grignard reagent from *o*-bromotoluene with D_2O in the standard way. The mass spectrum indicated 85% D.

4-Deuterio-1-methylnaphthalene was obtained by quenching the lithio derivative (*n*-butyllithium) from 4-bromo-1-methylnaphthalene with D_2O (80% D by mass spectrum).

Arylmethyl Bromides. Method 1. To 0.1 mol of the appropriate methylaromatic in dry CCl_4 (100 ml) was added *N*-bromosuccinimide (18.5 g) and a little benzoyl peroxide. The mixture was refluxed, and the progress of the bromination monitored by ^1H NMR spectroscopy (appearance of CH_2Br resonance at ca. δ 4.5) so that formation of dibromide ($-CHBr_2$) (ca. δ 6.6) was not significant. The cooled reaction mixture (0 °C) was filtered (to remove succinimide), and then washed with cold dilute NaOH solution and cold water (100 ml). The CCl_4 solution was separated, dried (Na_2SO_4), and then evaporated under reduced pressure. The arylmethyl bromide was either distilled or recrystallized for purification purposes.

***o*-Deuteriobenzyl bromide** was obtained in 76% yield (method 1).

1-Bromomethylnaphthalene (method 1) was furnished in 62% yield and two recrystallizations from hexane yielded material with mp 55–56 °C (lit.[14] 55–56 °C) showing ^1H NMR absorptions (CCl_4) at δ 4.71 (2 H, CH_2Br) and 7.2–8.0 (Ar).

4-Deuterio-1-bromomethylnaphthalene (method 1), % D ~ 80% (mass spectrum).

2-Bromomethylnaphthalene (method 1) was obtained as a white solid, mp 54 °C (lit.[15] 54–55 °C), after two recrystallizations from hexane: ^1H NMR (CCl_4) δ 4.46 (CH_2Br) and 7.2–7.7 (Ar).

6-Methyl-2-bromomethylnaphthalene was obtained from 2,6-dimethylnaphthalene using method 1, in 67% overall yield. The crude material was recrystallized twice from hexane to provide a white solid: mp 89–90 °C (lit.[14] 90 °C); ^1H NMR (CCl_4) δ 2.51 (CH_3), 4.63 (CH_2Br), 7.2–7.8 (Ar).

4-Bromomethylbiphenyl was obtained in 52% yield from 4-methylbiphenyl (method 1). After two recrystallizations from ethanol, a white, crystalline solid of mp 84–85 °C was obtained: ^1H NMR (CCl_4) δ 4.48 (CH_2Br), 7.4–7.6 (Ar).

Anal. Calcd for $C_{13}H_{11}Br$: C, 63.18; H, 4.46. Found: C, 63.01; H, 4.41.

9-Bromomethylanthracene (Method 2). To triphenylphosphine (2.8 g, 0.108 mol) in dry CH_3CN (20 ml) was added slowly bromine (1.6 g, 0.01 mol) until a faint persistence of the orange

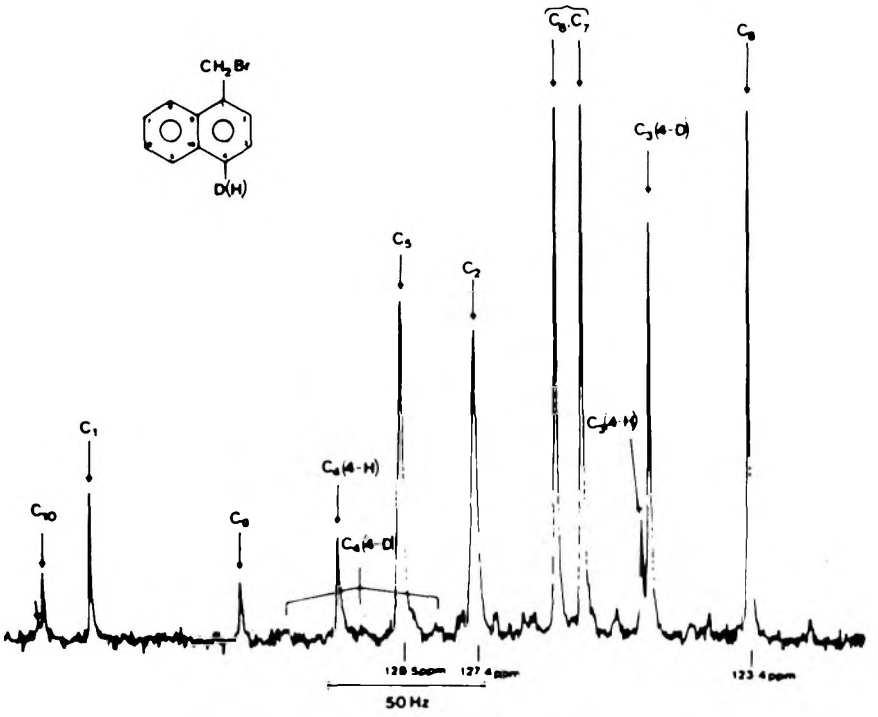


Figure 1. Proton decoupled ^{13}C spectrum (22.63 MHz) of 4-deuterio-1-naphthylmethyl bromide ($CDCl_3$ solvent). The deuterium isotope effect on the chemical shifts of C_4 and C_3 is apparent and results from incomplete 4-deuteration. The broadened signals correspond to C_2, C_5, and C_9 (compare with C_{10}) which are vicinal to 4-D, and experience ^{13}C–^2H coupling of ca. 1 Hz. A full listing of chemical shifts is given in Table I. (Methylene carbon resonance omitted.)

color. 9-Hydroxymethylanthracene (2.08 g, 0.01 mol) was added slowly (as a solid) and after about 1.0 g of the alcohol had been added, the solution became quite clear and a yellow solid then precipitated. The remainder of the alcohol was added, and the solution was stirred for an additional 1 h. The flask was cooled (0 °C) and the yellow solid was filtered and recrystallized from chloroform. The overall yield was 86%: mp 147–148 °C; ^1H NMR ($CDCl_3$) δ 5.46 (CH_2Br), 7.5 (H_2, H_3, H_6, H_7), 8.0 (H_4, H_5), 8.3 (H_1, H_8), and 8.4 (H_{10}).

Anal. Calcd for $C_{15}H_{11}Br$: C, 66.45; H, 4.06. Found: C, 66.47; H, 4.13.

NMR Spectra. ^{13}C spectra were obtained using a Bruker HX-90 spectrometer operating in the FT mode, and chemical shifts are relative to internal Me_4Si and accurate to ±0.05 ppm. Concentration effects on these ^{13}C shifts at the 10–20% concentration level were very small for tertiary carbons (i.e., CH) and were disregarded. ^1H NMR spectra were recorded on an MH-100 instrument for CCl_4 or $CDCl_3$ solutions with internal Me_4Si. Measurements of relaxation times (T_1) were conducted as previously described.[16]

Results and Discussion

^{13}C Shifts. A. Methylaromatics. The chemical shifts of all carbons in the parent methylaromatics are tabulated in Table I. For toluene, the assignments are secure[17,18] and in the case of 1-methylnaphthalene the only doubt involves C_6 and C_7,[19–21] but possible reversal of these shifts does not alter any conclusions. The assignments for 2-methylnaphthalene and 2,6-dimethylnaphthalene have been reported by two groups,[20,21] but our chemical shifts agree closely with those reported by Wilson and Stothers,[21] who also employed dilute solutions in $CDCl_3$. For 4-methylbiphenyl, the key 4 carbon was readily assigned by its relative intensity, while the other assignments were based on additivity considerations and agree with those already published.[22] The latter published data[22] were based on detailed statistical and parameterized analyses of substituent effects for a range of 4-substituted biphenyls. The assignments for 9-methylanthracene were based upon signal intensities, substituent effects, and chemical shifts and agree with those recently published[23] for enriched 9-methyl-9-^{13}C-anthracene.

B. Bromomethylaromatics. Assignments for the bromomethylaromatics are located also in Table I to facilitate comparisons with the methyl series. For benzyl bromide and 1-naphthylmethyl bromide, tactical deuteration (ortho and position 4, respectively) and consideration[19] of deuterium isotope effects on chemical shifts and ^{13}C–^2H coupling, led to the recorded assignments. The only possible ambiguity concerns C_6 and C_7 in the 1-naphthylmethyl bromide. A fully proton-coupled spectrum[19a] (67.8 MHz) of 1-naphthylmethyl bromide provided assignments absolutely consistent with those deduced from effects of deuterium substitution at the 4 position. "Multiplet patterns" due to long-range vicinal coupling (**C**–C–C–**H**) differ for carbons in different ring positions (Figures 1 and 2). C_3, assigned on the basis of a high-field 4-deuterium-induced shift in 4-deuterio-1-naphthylmethyl bromide, should appear as a sharp doublet in the ^1H-coupled spectrum, because C_3 is forbidden structurally from experiencing vicinal ^1H coupling. C_8, previously assigned at highest field on the basis of a substantial δ effect, appears as a doublet of doublets, with vicinal coupling to H_6. C_6 and C_7, expected to have very similar chemical shifts, appear as overlapping doublets of doublets, as anticipated for β carbons in such a benzo fragment. C_4, previously assigned by direct deuteration, experiences two different vicinal H couplings (H_2, H_5) and hence has a "pseudotriplet" appearance, in each component of the overall doublet (i.e., one-bond coupling). C_5, somewhat broadened in the (^1H decoupled) spectrum of the 4-deuterio compound, now displays a "broadened" doublet of doublets due to coupling to H_7 and H_4. H_2, previously assigned on the basis of braodening (vicinal ^2H coupling) in the 4-deuterio analogue, would be anticipated to exhibit considerable fine structure in each half of the (one-bond) doublet, as vicinal couplings to H_4 and $-CH_2Br$ are possible. This anticipation is realized in the form of "quartets" for C_2. The three quaternary carbons are not well resolved and these assignments in Table I are tentative. Nevertheless, the least coupled carbon would be C_1, and this agrees with the features of Figure 1. It is clear that proton-

Table I. Carbon-13 Assignments[a] for Methyl-and Bromomethylaromatics

Registry no.	Compd[b]	Carbon[b,c] 1	2	3	4	5(1′)	6(2′)	7(3′)	8(4′)	9	10	Other
108-88-3	Toluene	137.6	129.1	128.3	125.4	128.3	129.1					21.5
100-39-0	Benzyl bromide	137.9	129.1	128.8	128.4	128.8	129.1					33.1
	$\Delta\delta$[e]	+0.3	−0.0	+0.5	+3.0	+0.5	−0.0					11.6
90-12-0	1-Methylnaphthalene	134.2	126.6	125.5	126.6	128.6	125.4	125.7	124.1	132.7	133.6	19.3
3163-27-7	1-Bromomethylnaphthalene	132.0	127.4	125.0	129.3	128.5	125.8	126.2	123.4	130.8	133.7	31.5
	$\Delta\delta$[e]	−2.2	+0.8	−0.5	+2.7	−0.1	+0.4	+0.5	−0.7	−1.9	+0.1	12.2
91-57-6	2-Methylnaphthalene	126.9	135.4	128.0	127.3	127.8	125.0	125.9	127.6	133.6	131.8	21.6
939-26-4	2-Bromomethylnaphthalene	126.3	134.9	127.8	127.6	127.5	126.6	126.2	128.6	133.0	132.9	33.9
	$\Delta\delta$[e]	−0.6	−0.5	+0.3	−0.3	−0.3	+1.6	+0.3	+1.0	−0.6	+1.1	+12.3
581-42-0	2,6-Dimethylnaphthalene	126.6	134.3	128.1	127.0	126.6	134.3	128.1	127.0	132.1	132.1	21.5
52988-15-5	6-Methyl-2-bromomethylnaphthalene[d]	126.7	134.2	127.7	127.6	126.7	136.2	128.6	128.0	131.4	133.4	34.0, 21.6
		(126.2)	(134.1)	(127.9)	(127.6)	(126.6)	(136.2)	(128.5)	(128.0)	(131.2)	(133.1)	
	$\Delta\delta$[e]	+0.1	−0.1	−0.4	+0.6	+0.1	+1.9	+0.5	+1.0	−0.7	+1.3	+12.5

		1	2	3	4	5(1′)	6(2′)	7(3′)	8(4′)	9	10	11/14	12/13	Other
779-02-2	9-Methylanthracene	124.5	125.0	124.5	128.2	128.2	124.5	125.0	124.5	129.7	125.2	131.2	129.9	13.5
2417-77-8	9-Bromomethylanthracene	123.5	126.7	125.4	129.2	129.2	125.4	126.7	123.5	129.2	129.2	131.5	127.7	26.8
	$\Delta\delta$[e]	−1.0	+1.7	+0.9	+1.0	+1.0	+0.9	+1.7	−1.0	−0.5	+4.0	+0.3	−2.2	+13.3
644-08-6	4-Methylbiphenyl	138.5	127.0	129.5	136.8	141.4	127.0	128.7	127.0					21.0
2567-29-5	4-Bromomethylbiphenyl	140.3	129.7	127.4	136.7	141.8	127.0	128.7	127.4					33.1
	$\Delta\delta$[e]	+1.8	+2.7	−2.1	−0.1	+0.4	0	0	+0.4					+13.1

[a] Chemical shifts in parts per million downfield from Me_4Si. [b] IUPAC numbering adopted. [c] Numbering in parentheses applied to biphenyl system only. [d] Calculated values in parentheses. [e] The uncertainty in δ values is ±0.1 so the uncertainty in $\Delta\delta$ is ±0.2.

Table II. Calculated Changes in Charge Density (Δq) for $ArCH_3 \rightarrow ArCH_2^+$

System	Method	Carbon position[a] α	1	2	3	4	5(1′)	6(2′)	7(3′)	8(4′)	9	10	11	12	13	14
Benzyl	HMO	0.571	0.0	0.143	0.0	0.143	0.0	0.143								
	SCF-II	0.499	−0.076	0.142	0.035	0.222	0.035	0.142								
α-Naphthyl	HMO	0.450	0.0	0.200	0.0	0.200	0.050	0.0	0.05	0.0	0.050	0.0				
	SCF-II	0.381	−0.064	0.205	−0.009	0.263	0.092	0.046	0.133	−0.012	0.014	−0.049				
β-Naphthyl	HMO	0.522	0.232	0.0	0.058	0.0	0.0	0.058	0.0	0.058	0.0	0.058				
	SCF-II	0.440	0.227	−0.061	0.034	0.060	0.016	0.133	0.050	0.062	−0.036	0.074				
	SCF-II[b]	0.403	0.242	−0.064	0.046	0.047	0.010	0.148	0.048	0.064	−0.040	0.100				
4-Biphenylyl	HMO	0.512	0.0	0.128	0.0	0.128	0.0	0.032	0.0	0.032						
	SCF-II	0.437	−0.071	0.131	0.012	0.214	−0.080	0.037	0.027	0.086						
9-Anthrylmethyl	HMO	0.284	0.0	0.071	0.0	0.071	0.071	0.0	0.071	0.0	0.0	0.284	0.0	0.071	0.071	0.0
	SCF-II	0.270	−0.010	0.138	0.033	0.090	0.090	0.033	0.138	−0.010	−0.056	0.304	−0.065	0.056	−0.056	−0.065

[a] IUPAC numbering adopted. Numbering in parentheses refers to biphenyl system only. For naphthyl systems $C_{10} = C_4a$ and $C_9 = C_8a$. [b] Self-consistent in bond lengths.

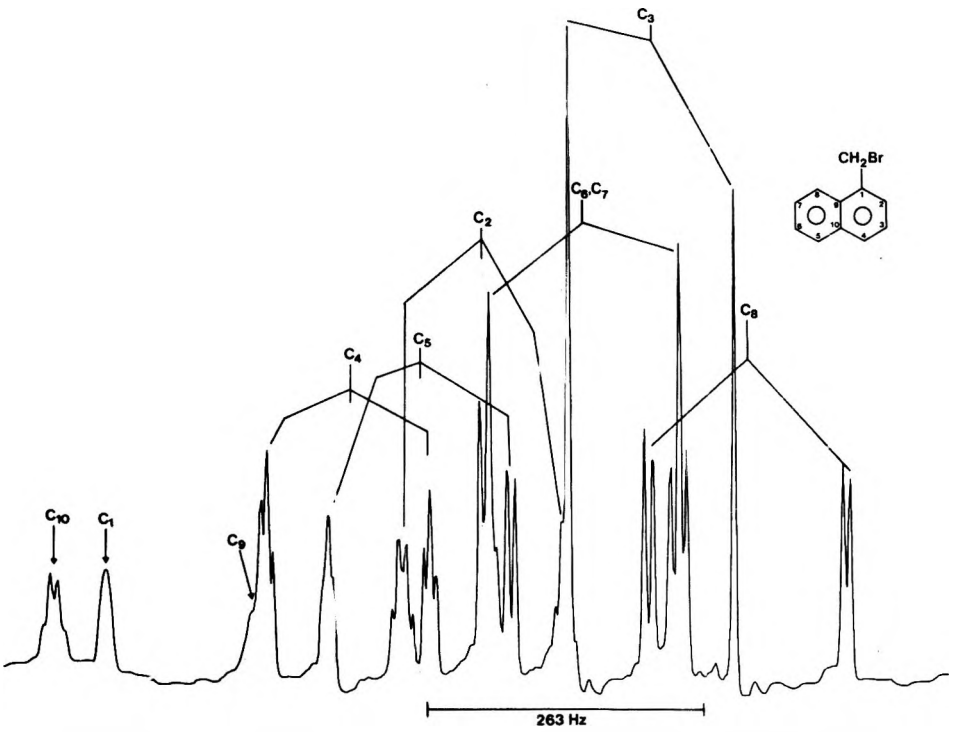


Figure 2. Proton *coupled* spectrum of 1-naphthylmethyl bromide at 67.89 MHz ($CDCl_3$ solvent) illustrating the characteristic coupling patterns. Assignments are as marked and correspond with those in Figure 1. The low-field half of the C_4 doublet is superimposed on a quaternary carbon resonance. (Methylene carbon resonance omitted.)

coupled spectra provide an additional and powerful approach for assignments in substituted naphthalenes, and complement the effects of specific deuterium substitution.

For 2-alkyl substituted naphthenes additivity effects on ^{13}C shifts have been established.[20,21] The procedure then was to assign as reasonably as possible the spectrum of 2-bromomethylnaphthalene and knowing the effect of 2-methyl substitution at all positions in naphthalene, to calculate the signal positions for 6-methyl-2-bromomethylnaphthalene, using the chosen assignments for the 2-bromomethyl compound. These assignments were then adjusted until the calculated and observed signals for the 6-methyl-2-bromomethyl compound harmonized. No deviation greater than 0.5 ppm occurred, and except for two positions, deviations were 0.2 ppm or less. No other combinations could afford such impressive consistency, and we regard the assignments for these systems as established. The 4′ carbon in 4-bromomethylbiphenyl was identified by its relative intensity compared with other tertiary (protonated carbons). The effects of the $-CH_2Br$ group at ring positions in benzyl bromide were applied to the directly attached ring in the biphenyl compound. Additivity considerations of phenyl and $-CH_2Br$ substitution on benzene shifts then led to the indicated allocations For 9-bromomethylanthracene, C_{10} was identified by its intensity (22.6 and 67.8 MHz spectra) relative to other tertiary carbons. Other assignments were based essentially on compressional and chemical shift arguments, and, while in all probability correct, cannot be regarded as definitely established. Our main concern in this system was with C_{10}.

Quaternary carbons in all systems were identified by their characteristically lower intensities and longer relaxation times and in some cases, quite positively assigned by deuterium effects on the spectra and substituent chemical shifts. The CH_3 and $-CH_2Br$ signals were the only ones at higher field.

An assessment of the substituent effect of $-CH_2Br$ requires comparison with the corresponding methylaromatic, and the chemical shift changes ($\Delta\delta$) for all carbons in these systems, associated with the structural change $ArCH_3 \rightarrow ArCH_2Br$, are tabulated in Table I. For purposes of analysis, data pertaining to ortho-type positions are rejected since steric and compressional effects at these sites may mask any bona fide electronic effect. The data in Table I show quite definitely the deshielding effect of CH_2Br (vs. CH_3) at conjugative unencumbered positions[24] and in view of available evidence[9-12] relating ^{13}C shift and π-charge density, $\Delta\delta$ is logically associated with removal of such charge density by the C–Br bond. A very striking aspect of the data in Table I is the variation in $\Delta\delta$ with the nature of the aryl group in $ArCH_2Br$.

The Theoretical Model. The above dependence of $\Delta\delta$ on the aryl system in $ArCH_2Br$, and previous information[7] indicating a strong stereoelectronic dependence of C–X substituent effects generally, pointed to a σ–π or hyperconjugative mode[25] of π-charge removal by $-CH_2Br$. Therefore it seemed attractive to examine the $\Delta\delta$ trends with Ar in the framework of a conjugative model. Considering that the hyperconjugative effect is due to interaction of aryl ring MO's with the (polarized) C–Br σ-bonding MO, a very simplified approach would be to use $ArCH_2^+$ as the model, and obtain a measure of the transmission of mesomeric effects between ring positions and CH_2. The ^{13}C shift differences ($\Delta\delta$) are taken as a reflection of π-charge levels in the immediate region of the carbon atom.

π-Charge Densities in $ArCH_2^+$. A. HMO Technique. The special properties of the NBMO of odd alternate hydrocarbon systems $ArCH_2$ allow ready calculation of the NBMO coefficients (a_{0i}) at the more numerous "starred" set of atoms.[26,27] In an odd alternant cation, the charge density is $(1 - a_{0i}^2)$, a_{0i} being the NBMO coefficient of atom i.[27] In Figure 3 the quantity $\Delta\delta$ is plotted against the change in charge density (Δq), a_{0i}^2. The data for the 6-methyl-2-naphthyl system (Table I) have not been plotted, but the trends in $\Delta\delta$ for C_6, C_8, and C_{10} (and other positions) closely parallel those for the parent 2-naphthyl sys-

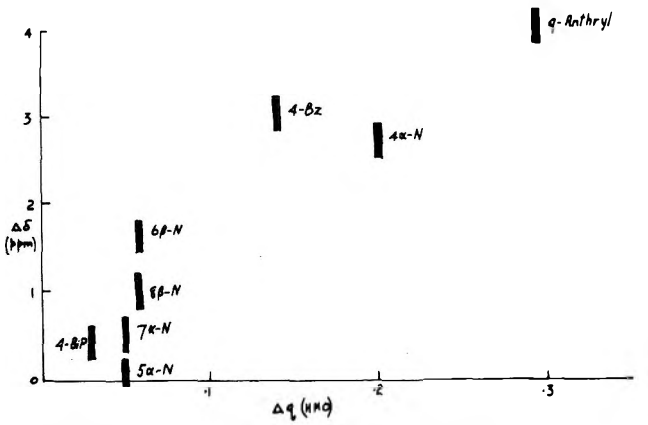


Figure 3. Plot of carbon-13 chemical shift changes ($\Delta\delta$) for the change $ArCH_3 \rightarrow ArCH_2Br$ at the indicated ring positions against the HMO-derived changes in π-charge density (Δq) at those sites. The heights of rectangular "points" correspond to uncertainties (±0.2 ppm) in $\Delta\delta$. Statistical treatment of the data (omitting 4-biphenyl, 5α- and 7α-naphthyl data) yields a correlation coefficient of 0.93, significant at the 95% level. Inclusion of the 4-biphenyl datum yields $r^2 = 0.94$, significant at the 99% level. The best straight line in the latter circumstance has an intercept of 0.44 (Y axis) and passes through $X = 0.20$, $Y = 3.05$.

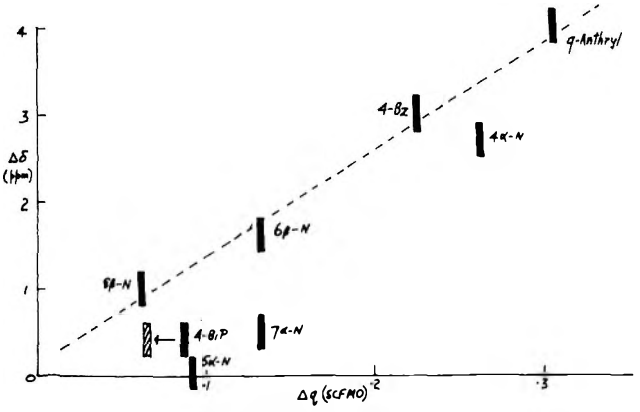
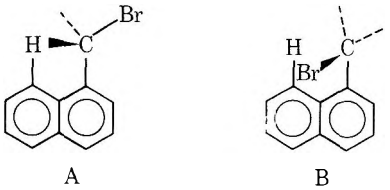


Figure 4. Plot of carbon-13 chemical shift changes ($\Delta\delta$) for the change $ArCH_3 \rightarrow ArCH_2Br$ at the indicated ring positions against the SCF-π derived changes in π-charge density (Δq) at those sites. The heights of rectangular "points" correspond to uncertainties (±0.2 ppm) in $\Delta\delta$. The hatched rectangle for 4-biphenyl corresponds to $\Delta q = 0.065$ calculated for an interannular angle of $\theta = 45°$. Statistical treatment of the data (including the "hatched" 4-biphenyl datum but omitting 5α- and 7α-naphthyl data) yields a correlation coefficient $r^2 = 0.96$, significant at the 99% level. The best straight line has an intercept $Y = 0.11$ and passes through $X = 0.20$, $Y = 2.46$. Treatment of all data (in Figure 4) (eight observations) yields $r^2 = 0.92$, again within the 99% level. The intercept is now $Y = 0.67$, and the best line passes through $X = 0.2$, $Y = 2.26$.

tem. Data for quaternary carbons have not been employed as we and others[21,28] have noted that these carbons are far more sensitive to concentration and bond-order changes. In these circumstances, the prudent course seemed to be to confine attention to tertiary carbons but it should be noted that $\Delta\delta$ values for quaternary carbons (Table II) are not glaringly out of line with $a_{0i}{}^2$. The data for positions 2 and 4 in anthracene are not plotted owing to the unproven nature of these assignments.[29]

The general dependence of $\Delta\delta$ on $a_{0i}{}^2$ (in Figure 3) is immediately apparent, and, considering the gross nature of this treatment, constitutes impressive evidence for a conjugative mode of electron withdrawal by the C–Br bond. Several pieces of data are somewhat poorly correlated, particularly the points 7α-naphthyl, 4-biphenyl, and 5α-naphthyl. We shall see that these deviations have a most convincing explanation or agreement with other experiment, that strengthens the general conclusion.

The $\Delta\delta$ values for 4-benzyl and 4α-naphthyl are of interest, as although all treatments of conjugative interactions in these positions show 4α-naphthyl to be superior,[30] the $\Delta\delta$ values are, within error (±0.2 in $\Delta\delta$), identical (2.7 and 3.0 ppm). The explanation in part may involve the regulating action of the peri hydrogen (at position 8) on the conformational populations of the $-CH_2Br$ system in the α-naphthyl case. That conformation drawn below (A) may be



favored as it most effectively alleviates nonbonded 8H–Br interactions, but this geometry prohibits (hyperconjugative) σ C–Br-π mixing, which is pronoted, however, in B. More extensive studies of these effects are proceeding. These effects on properties of other α-naphthyl and related systems have been well documented.[31,32] Since A represents an energy well for rotation about C_1–CH_2 bond, it seemed that evidence for an exalted population of this conformer might result from T_1 (relaxation time) measurements of the methylene carbon. Such an experiment would be definitive if the rate of overall molecular reorientation was less than the rate of $-CH_2Br$ group rotation for benzyl bromide but faster in the 1-naphthyl derivatives.[33] Direct comparison of $-CH_2Br$ T_1 values in the two cases is not valid because the overall molecular microdynamics are different. However, it should be possible to compare T_1 ($-CH_2Br$)/T_1 (backbone) in the two cases to indicate any differences in CH_2Br group rotation. When this is done we conclude that in both cases the rate of CH_2Br rotation is slower than that of overall reorientation. This result is to be compared with other T_1 studies on CH_3 group rotation where the internal motion of the CH_3 group is important.[34] We conclude that, in general, the rotation of CH_2Br is much slower, probably the consequence of a larger moment of inertia.

For 1-naphthylmethyl bromide, ^{13}C spectra were recorded at 323 K (50 °C) and 223 K (−50 °C), in the expectation that conformation A would experience significant population changes, with attendant variations in the ^{13}C chemical shifts.[35] Over this temperature range, however, the changes were very modest indeed,[36] and not reliably interpreted.[37] The barrier to CH_2Br rotation seems to be low and would require study at much lower temperatures. Here, however, the problems of aggregation and molecular ordering could be most distressing.[38]

As indicated above, the point for 5α-naphthyl appears to be disturbingly misbehaved, particularly since both HMO and SCFMO calculations place significant charge density in odd AH systems at this site. However, for this disposition in naphthalene, experiment is well ahead of theory since the evidence (both NMR and reactivity studies) is overwhelming that any conjugation here is trifling. For example, Schreiber and Byers[39] demonstrated that whereas 1-chloromethyl-4-methoxynaphthalene solvolyzes 38×10^4 times faster than 1-chloromethylnaphthalene, 1-bromomethyl-5-methoxynaphthalene solvolyzes only 2.4 times as fast as 1-bromomethylnaphthalene. More recently, in an extensive assessment of ^{19}F SCS in naphthyl systems, Adcock and co-workers[40] reported that replacement of the hydrogens in NH_2 by CH_3 groups in 1-fluoro-5-aminonaphthalene produced a negligible effect, confirming the ab-

sence of 1,5 mesomerism.[41] Hence this lack of correlation in Figure 3 for 5α-naphthyl is in fact consoling and additional support that $-CH_2Br$ is mimicking the behavior of other authentic conjugating substituents.[42] Deviations for 7α-naphthyl and to a lesser extent 8β-naphthyl are also apparent. Regarding the biphenyl system, the lack of correlation was anticipated, since the value of a_{0i}^2 (Δq) is based on an assumed planar molecule, which is certainly incorrect for the liquid phase.[5] Other assumptions regarding geometry, e.g., interannular bond length, and a general overestimation of mesomerism to the second ring, also contribute.

B. SCFMO Approach. While the foregoing HMO-based treatment provides a convincing analysis to the problem, it was considered desirable to obtain π charges by a more rigorous SCFMO approach, with particular hope that some of the deviant data may be "rescued". A program was already available[43] which assigns the exocyclic C–C bond the fully conjugated benzene bond length of 1.39 Å, and which treats all C–C lengths as such. In the biphenyl case, a planar geometry was assumed and the interannular bond was assigned a length of 1.39 Å. This procedure has had impressive success[44,45] in correlating other spectral parameters and details of the method can be found elsewhere.[27,46] In Figure 4, the quantities $\Delta\delta$ correlate exceptionally well with the SCFMO π-charge densities (Δq), except for 4α-, 7α-, and 5α-naphthyl and 4-biphenyl. Cogent reasons for these deviations have been presented (vide infra), but it is apparent that the 5α disposition in naphthalene cannot be regarded as a "conjugated" position, and more refined calculations are required to reproduce experimental facts in the second ring of α-naphthyl systems. The situation is that inter-ring communication for some dispositions, notably 5α, is far less than available calculations indicate. Treatment[40] of substituent behavior by the DSP approach[47] (Dual Substituent Parameter) at various positions provides the following sensitivity factors for resonance: 4α, −31.42; 6β, −12.54; 7α, −4.43; 8β, −4.71; and 5α, +0.096. These parameters correspond generally with π charges (or mesomeric transmission factors) listed in Table II, except for 7α and 5α, which we have noted are poorly correlated in Figures 3 and 4.[49] Reduction in the value of a_{0i}^2 for 4-biphenyl to a more realistic value,[48] e.g., 0.065, indicates acceptable behavior for this system. A somewhat interesting conclusion from Figure 4 is that any component of $\Delta\delta$, other than the hyperconjugative one, must be quite small as the best correlation line passes very close to the origin.

The HMO and SCF π charges employed are located in Table II.

Previously, the demonstration was made[5] that the ^{19}F NMR substituent chemical shifts for bromomethyl substituted flurorayl systems correlated handsomely with the π-charge densities in the benzyl, α- and β-naphthyl, and 4-biphenyl systems. In view of the general correspondence between ^{13}C and ^{19}F SCS in aryl systems in situations of strong conjugation, e.g., 4α, 6β [40] it is reassuring that in the present cases this type of dependence is also observed.

In general, the trends in Table III can be rationalized on the basis that ^{13}C and ^{19}F SCS incorporate a different blend of mesomeric and field effects, with the latter more important for ^{19}F SCS. For example, the increase in the ^{19}F SCS on proceeding from 4-benzyl to 4α-naphthyl (Table III) is in all probability due to an increase in the π-polarization component of the field effect which apparently compensates for any reduction in C–Br hyperconjugation. The ^{13}C probe, on the other hand, being less influenced by field effects, more effectively reflects the reduction in C–Br hyperconjugation.

Table III. ^{19}F and ^{13}C SCS for Arylmethyl Bromides

Disposition	^{19}F SCS	^{13}C SCS
4-Benzyl	5.07	3.0
4α-Naphthyl	5.60	2.7
6β-Naphthyl	2.48	1.6
4,4'-Biphenyl	0.89	0.4

If $-CH_2Br$ is conjugatively electron withdrawing, how then can we rationalize greatly preferred ortho–para electrophilic substitution in benzyl halides?[2] The answer lies in the potentially multicomponent nature of the overall CH_2X substituent effect:[7] (a) hyperconjugative electron withdrawal by the C–halogen σ bond; (b) hyperconjugative electron release by C–H σ bonds; and (c) electron withdrawal by an inductive field effect. (For an essentially noncharged polar system this latter effect is minor). Depending on the confirmation of CH_2X with respect to the ring, it is clear that either a or b could be dominant. In aromatic electrophilic substitution which appreciable charge development, rotation about the C–C bond generates an arrangement favoring C–H electron release, but essentially prohibiting C–X electron withdrawal. In the neutral ground state, however, it seems reasonable that the conformation favoring C–Br electron withdrawal will be favored. Careful vibrational spectroscopic studies of arylmethyl halides could prove illuminating in this regard.

The change $ArCH_3 \rightarrow ArCH_2Br$ results in downfield shifts of ca. 12–13 ppm for C_α, somewhat less than the normal "α" effect of bromine substitution (~20 ppm) in saturated alkyl systems.[50] A rehybridization effect, $sp^3 \rightarrow sp^2$, with charge deficiency[51] may be partly responsible, but other "special" effects may also contribute. The $\Delta\delta$ values for ipso carbons are irregular and small, and "special" influences of various sorts would need to be considered, in addition to π-charge variations.

While we believe that the present data pertaining to the ground-state behavior of CH_2Br groups are most persuasive, final justification must await ^{13}C chemical shifts particularly for α- and β-naphthylmethyl cations. Our analysis would predict (a) a feeble interaction at C_5 in the α cation and (b) an essentially linear correlation between our $\Delta\delta$ values for $ArCH_2Br$ (vs. $ArCH_3$) and $\Delta\delta$ for $ArCH_2^+$ vs. $ArCH_3$. Further studies of conformationally constrained arylmethyl systems are in progress.

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Registry No.—*N*-Bromosuccinimide, 128-08-5; 9-hydroxymethylanthracene, 1468-95-7.

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(36) C_4 appears to have undergone no shift change, while C_8 and C_α have suffered −0.02 and +0.9 ppm shifts, respectively.
(37) The proton spectrum of 1-naphthylmethyl bromide has been examined at lower temperatures [M. D. Bentley and M. J. S. Dewar, *J. Org. Chem.*, **35**, 2707 (1970)] and over the range 40 to −100 °C, the $-CH_2Br$ resonance suffered a 0.4 ppm low-field shift. This was interpreted in terms of a steric effect displacing the Br group out of the plane of the ring, apparently implying B to be favored at lower temperatures. However, the possibility of significant molecular layering at lower temperatures and the effects of specific molecular organization would need careful evaluation. The effects of lower temperatures on the ring-proton shifts were not discussed, but may have indicated aggregation, or specific collision complexes.[38]
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(41) (a) For a discussion and examples of the effect of this structural manipulation on mesomerism in other naphthyl systems see W. Adcock and M. J. S. Dewar, *J. Am. Chem. Soc.*, **89**, 379 (1967). (b) The ^1H NMR spectra of arylmethyl anions have been investigated in some detail [F. J. Kronzer and V. R. Sandel, *Chem. Ind. (London)*, 210 (1972); F. J. Kronzer and V. R. Sandel, *J. Am. Chem. Soc.*, **94**, 5750 (1972); V. R. Sandel and H. H. Freedman, *ibid.*, **85**, 2328 (1963)], and in the case of 1-naphthylmethyllithium (THF) (compared with 1-methylnaphthalene[21] in $CDCl_3$) H_4 and H_5 suffer high-field shifts of 1.90 and 0.74 ppm, respectively. These relative shifts are in somewhat poor agreement with HMO parameters (0.200 and 0.05, respectively) but more agreeably with SCF-π parameters (0.263 and 0.092, respectively) (Table II). Ion pairing and specific molecular aggregation could be troublesome, as could the known sensitivity of ^1H shifts to long-range magnetic perturbations of various kinds. In addition, substantial field effects may also operate in addition to any conjugation. Careful studies of the ^{13}C spectra of 1- and 2-naphthylmethyllithium would be most informative.
(42) There is evidence (ref 40) that in the case of ^{19}F shielding in the 5α-naphthyl system, field effects and steric crowding may contribute to the overall ^{19}F SCS. These would be less important for ^{13}C SCS.
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(49) We at first suspected that the assumptions regarding bond lengths in the naphthyl framework may have been partly to blame for the overestimation of mesomerism to the second ring. A calculation with self-consistency in bond lengths was not enlightening, and if anything, aggravated the situation. More thorough (and expensive) calculations are required.
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Evidence for Free-Radical Reductive Dehalogenation in Reaction of Zinc and Acid with 1-Perfluoroalkyl-2-iodoalkanes and with 1-Perfluoroalkyl-2-iodoalkenes[1]

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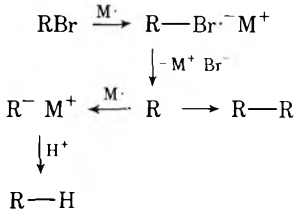
Reductive dehalogenation of 7-perfluorobutyl-6-iodo-1-heptene by either tri-*n*-butyltin hydride or zinc and acid gave partial cyclization to *cis*- and *trans*-1-methyl-2-(perfluorobutyl)methylcyclopentane, and at a rate consistent with previously studied free-radical cyclizations. Cyclization was slower for 8-perfluorobutyl-7-iodo-1-octene, while 6-perfluorobutyl-5-iodo-1-hexene gave only unrearranged product. Reductive dehalogenation of 1-perfluoropropyl-2-iodo-1-hexene was not stereospecific but inversion of the intermediate vinyl radicals occurred. Free-radical addition of perfluoropropyl iodide to 1-heptyne did not give internal hydrogen transfer and cyclization as had been observed for analogous reaction of CCl_4 or of $HCCl_3$.

The purpose of this research was (1) to synthesize iodine-free perfluoroalkyl-substituted alkanes and alkenes of various types; (2) to compare the behavior of a homologous series of 1-perfluoroalkyl-2-iodo terminal alkenes and of 1-perfluoroalkyl-2-iodo-1-alkenes during dissolving metal reduction, in which free radicals might be involved; and (3) to compare reductive dehalogenation of tri-*n*-butyltin hydride with that given by zinc and acid in this series of compounds.[2]

It is important to recognize that in most chemical reactions the perfluoroalkyl group retains its integrity, as a result of the high C–F bond strength. Rearrangement, loss of

fluorine, or C–C bond cleavage are seldom observed. Hence, reductive defluorination is not anticipated in these reactions, in which C–I bonds are broken.

By way of background it would be helpful to review the state of the art as summarized in a recent text. "The mechanism of carbon–halogen cleavage has been studied extensively for reductions effected with solutions of alkali metals, with chromium(II) salts, zinc, magnesium and iron, and by electrolysis. Dissolving metal reductions are considered to involve transfer of an electron from the metal surface (or from metal in solution), or from a lower valence state of certain metal ions, e.g. Cr(II). Such reactions are probably related to the formation of organometallic derivatives (or dimeric products) when alkyl halides are allowed to react with metals. The possibility that free radicals or organometallic derivatives may be short-lived intermediates in these reductive cleavage reactions is suggested, since elimination rather than cleavage is usually observed if a substituent (halogen, –OH, –OR, –OCOR) that can be lost as a stable anion is present at an adjacent carbon atom."[2] The reaction paths have been diagrammed as follows.[3]



Results

Free-radical addition of iodoperfluoroalkanes (R_FI) to terminal alkenes provided novel 1-perfluoroalkyl-2-iodoalkanes in excellent yield.[4] Similar reaction with 1-alkynes gave (*Z*)- and (*E*)-1-perfluoroalkyl-2-iodo-1-alkenes (**1a,b** and **2a,b**). Addition was stereoselective but not stereospecific as it was formerly believed to be.[4] In the case of terminal alkadienes, structure of the reaction product depended on the distance between the end groups. With 1,6-heptadiene cyclization of the intermediate radical occurred in part and a mixture of open-chain (**3**) and cyclic products (**4**) was isolated[5] (Chart I). While reductive dehalogenation of certain 1-perfluoroalkyl-2-iodoalkanes by zinc and acid has already been described,[4-7] evidence has now been obtained which tends to confirm the suspected free-radical nature of the process.

In orientation experiments 2-iodooctane and 5-iodo-1-hexene were dehalogenated using the well-known free-radical reducing agent, tri-*n*-butyltin hydride (TBTH).[8] Reduction in both cases gave the normal products (*n*-octane and 1-hexene). With 7-perfluorobutyl-6-iodohept-1-ene (**3**), however, a substantial amount of cyclization occurred (Chart II). Gas–liquid phase chromatography showed that 32.5% of open-chain product **5** was formed and 67.5% of cyclic product **6a,b**; the ratio of **5**/**6** was 0.480. This is consistent with abundant evidence from previous studies[9-12] showing the intermediacy of radicals in this reaction. The next higher homologue, 8-perfluorobutyl-7-iodooct-1-ene (**7**), with TBTH gave 98% of linear product **8** and not more than 2% of cyclic product **9a,b**.

These same reductions were then performed using zinc and acetic acid in ether as the reducing system;[13] see Chart III. 6-Perfluorobutyl-5-iodohex-1-ene (**10**) gave only open-chain product **11**. There were no extraneous peaks in GLC analysis and the NMR spectra showed no methyl group resonance. However, **3** again cyclized during reduction and the ratio of **5**/**6** formed was 0.297. Area measurements in GLC analysis and NMR spectra were in good agreement.

Chart I. Preparation of 1-Perfluoroalkyl-2-iodo-1-alkenes and of 7-Perfluoroalkyl-6-iodohept-1-ene and 1-Iodomethyl-2-(perfluoroalkyl)methylcyclopentanes

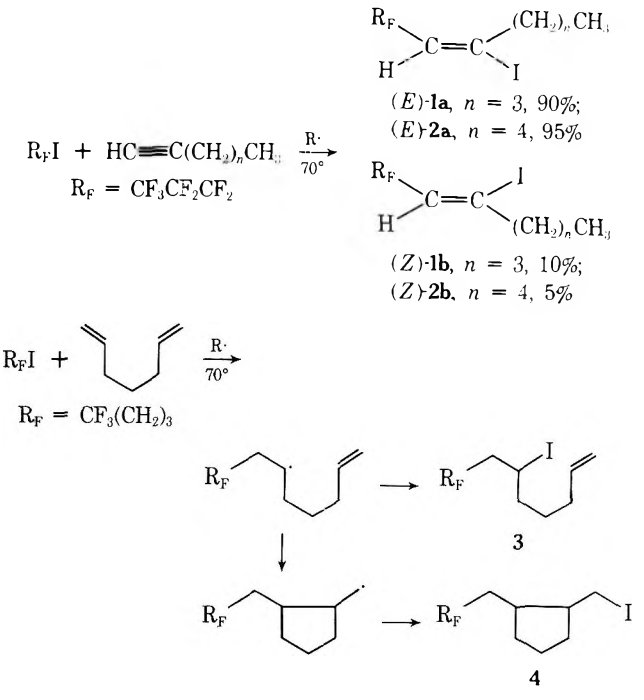
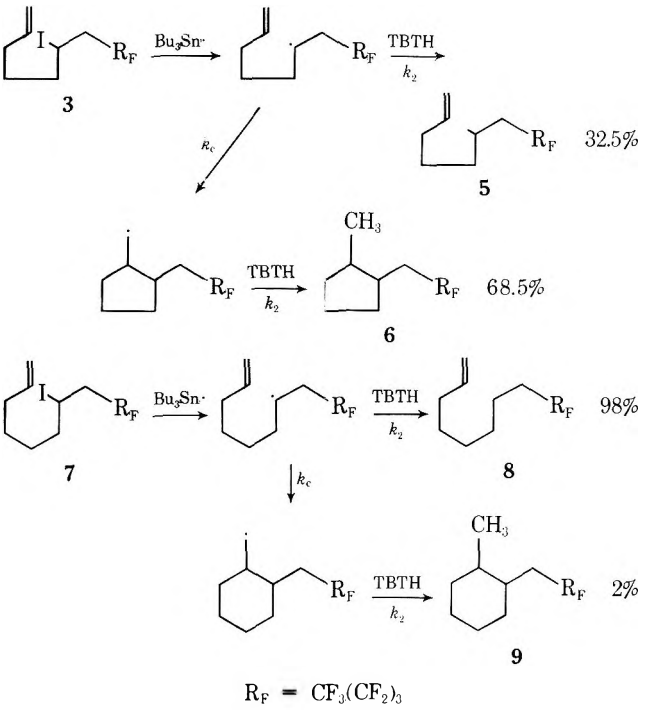


Chart II. Tri-*n*-Butyltin Hydride Reduction of Iodoalkenes

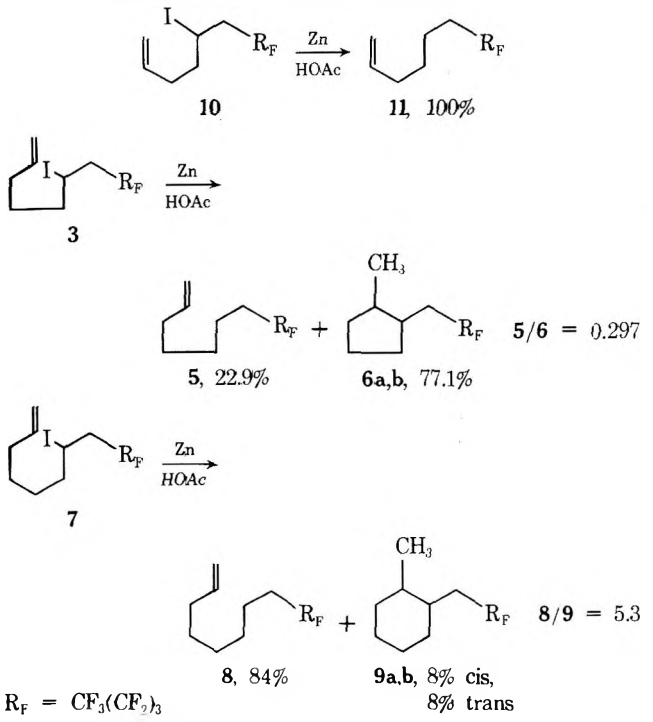


Proton resonances for the CH_3CH coupling (doublet, J = 7 Hz) in the cis and trans isomers of **6** were clearly defined; cis/trans = 1:2. Zinc reduction of **7** gave a significant amount of cis and trans isomers of 1-methyl-2-(perfluorobutyl)methylcyclohexane (**9a,b**). Proper choice of GLC column and operating conditions permitted separation of two peaks of identical area (8.0%). NMR spectra also showed the expected resonances for two methyl groups, and ir spectra gave CH_3 group absorption bands.

Clearly, reductive dehalogenation of iodoalkenes by zinc and acid has characteristics of a free-radical process.

Reduction of 1-Perfluoroalkyl-2-iodo-1-alkenes. De-

Chart III. Zinc and Acid Dehalogenation of Iodoalkenes

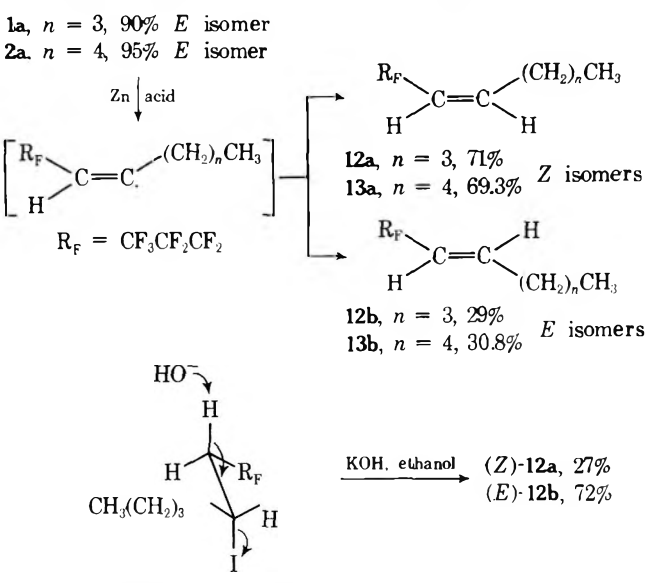


halogenation of 1-perfluoroalkyl-2-iodo-1-alkenes afforded additional evidence for the intermediacy of free radicals. 1-Perfluoropropyl-2-iodo-1-hexene (90% *E* isomer, **1a**) gave $CF_3CF_2CF_2CH{=}CH(CH_2)_3CH_3$, 71% *Z* isomer **12a**, and 29% *E* isomer **12b**, by reaction with zinc and hydrogen chloride in alcohol solution at 78° (Chart IV). A similar reaction of 1-perfluoropropyl-2-iodo-1-heptene (95% *E* isomer **2a**) gave reduction to 1-perfluoropropyl-1-heptene, 69.3% *Z* isomer **13a** and 30.7% *E* isomer **13b**. These reactions show that a substantial loss of configuration occurs during reduction. Evidence for structures was obtained by synthesis of **12a,b** from 1-perfluoropropyl-2-iodohexane (**14**) by dehydrohalogenation. Isomers of **12a,b** obtained by GLC trapping were distinguished by their ir spectra; *Z* isomer **12a** had double bond stretching frequency at 1660 cm^{-1} and *E* isomer **12b** had this band at 1680 cm^{-1}. Two additional points of interest should be noted. Exclusive α-dehydrohalogenation was observed, as shown by the identity of **12a,b** obtained from **1a,b** and from **14**, and the absence of significant side products (GLC analysis). There was a preference for *E* isomer **12b**, from anti elimination of **14** in the conformation having the R_F and alkyl groups also anti to each other, to minimize crowding. The ratio of **12a/12b** was 1:2.67.

In most of these experiments using zinc and acid small amounts of higher boiling products were formed. They are believed to be the result of radical coupling, as indicated previously. Such products have been frequently obtained and appear to be favored by slow reaction and minimal contact of the iodoalkane at the reacting metal surface. These are conditions which would obtain in a two-phase liquid system. A further example is the reduction of 1-perfluoroheptyl-2-iodohexadecane (**15**) in benzene and aqueous hydrochloric acid by zinc and magnesium powder to 1-perfluoroheptylhexadecane (**16**) in 62% yield and to 15,16-[bis(perfluoroheptyl)methyl]triacontane in 28% yield.

The homogeneous organic phase which is formed using an anhydrous alcohol and hydrogen chloride (gas) has given less coupling, rapid reaction, and high yields of reduced, uncoupled product (85–92%).[14,15] In several of the experiments reported herein the solvent system acetic acid–

Chart IV. Nonstereospecific Reduction of 1-Perfluoroalkyl-2-iodo-1-alkenes. Exclusive α-Dehydrohalogenation of 1-Perfluoroalkyl-2-iodoalkanes



14 (preferred conformation)

diethyl ether, recommended by Hassner,[13] was used with good success. However, removal of the acetic acid was somewhat troublesome. It may be of interest to note that in one attempted Grignard reaction using *endo*-2-iodo-*exo*-3-perfluoropropylnorbornane, where crowding may have been a problem, a good yield of coupling product, 2,2′-bis(3-perfluoropropylnorbornyl), was obtained.[6] Here, too, loss of configuration occurred, as two forms having syn and anti fusion of the two rings were isolated.

Discussion

These experiments closely link the solid evidence[9–12] for free-radical mechanism of dehalogenation by TBTH with the zinc and acid heterogeneous systems we have frequently used. Since the rate constant for transfer of hydrogen from TBTH to an alkyl radical was determined[10] to be $k_2 = 1.1 \times 10^6\ M^{-1}\ sec^{-1}$ at 25°, it is possible to estimate the rate constant for cyclization at 50° of **3**:

$$5/6 = k_2/k_c[\text{TBTH}];\ k_c = 4 \times 10^6\ M^{-1}\ sec^{-1}$$

For the 5-hexenyl radical $k_c = 1 \times 10^{-1}\ sec^{-1}$ and for the 4-(cyclohexenyl)butyl radical $k_c \simeq 4 \times 10^4\ sec^{-1}$.[10] The rate constant for cyclization of **7** at 50° is similarly

$$8/9 = k_2/k_c[\text{TBTH}];\ k_c = 4 \times 10^4\ sec^{-1}$$

These values are indeed close to the previously determined constants for related reactions.

By comparing the **5/6** ratio in zinc reduction of **3** with that obtained in TBTH reduction we may estimate the "effective concentration" of active reducing agent. Using the calculated value for k_c we have

$$5/6 = 0.297 = \frac{1.0 \times 10^6}{4 \times 10^6}\ [\text{reducing agent}]$$

From this the [reducing agent] is found to be about 1.2 *M*. The iodooctene **7** yields an estimate for [reducing agent] of about 0.21 *M*. Of course, one would expect that the "effective concentration" would vary widely according to the experimental conditions employed.

It had previously been reported[16] that zinc and acid gave stereospecific reduction of 1-perfluoroalkyl-2-iodo-1-alkenes such as **1a,b** and **2a,b**. The present results show that such is not the case. It was necessary to be able to separate

Table I
Sources and Physical Constants of Starting Materials

Compd	Code	Bp, °C (mm)	$n^{25}D$	Source
Tri-*n*-butyltin hydride		80 (0.50)		ref 20
5-Iodo-1-hexene		38–40 (15)	1.5100	ref 22
$CF_3CF_2CF_2CH{=}CI(CH_2)_3CH_3$	1a,b	94 (50)	1.4095	ref 4
$CF_3CF_2CF_2CH{=}CI(CH_2)_4CH_3$	2a,b	95 (25)	1.4135	This paper
$CF_3(CF_2)_3CH_2CH(CH_2)_3CH{=}CH_2$ I	3	90 (8)	1.4065	ref 6
$CF_3(CF_2)_3CH_2CHI(CH_2)_4CH{=}CH_2$	7	56 (0.25)	1.4080	ref 21
$CF_3(CF_2)_2CH_2CHI(CH_2)_3CH_3$	14	85 (23)	1.4029	ref 23

the two isomers by GLC, since the ir spectra could not be used to distinguish them in a mixture. Both *Z* and *E* isomers of **1** or **2** had the double bond stretching frequency at 1640 cm^{-1}. Once the two isomers were separated the fingerprint region did show significant differences. The reduced product **12a,b** from **1a** was more readily identified by ir, but there was considerable merit in using the more accurate and sensitive GLC method to determine product composition.

Isomerization of the vinyl radical from **1a** or **2a** is not expected to be a high-energy process. Similar radicals also equilibrate. Hay summarizes some recent work involving isomerization and cyclization of substituted vinyl radicals.[17] In this connection it was surprising to find that radical addition of R_FI to 1-heptyne did not give any cyclization product analogous to that obtained by Heiba and Dessau in the reaction of CCl_4 or $HCCl_3$ with 1-heptyne.[18] It appears that the rate of transfer from R_FI to the intermediate vinyl radical is considerably faster than hydrogen abstraction. This finding may in fact make it possible to determine rate constants for transfer from these small molecules to carbon radicals.

Experimental Section[19]

Source of Materials and Physical Measurements. Table I lists the sources and physical constants of starting materials. TBTH was prepared from tri-*n*-butyltin chloride (Aldrich) and lithium aluminum hydride (Ventron) in 52% yield,[20] and redistilled in a 3-ft spinning band column. Less pure material did not react properly. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were done using a Varian A-60 spectrophotometer. Gas chromatographic analyses were performed using a Sargent-Welch thermal conductivity or a Perkin-Elmer Model 881 unit fitted with a hydrogen flame detector, and under conditions which are listed as appropriate.

Reduction of 5-Iodo-1-hexene with Tri-*n*-butyltin Hydride. A 50-ml flask was fitted with a variable takeoff, total reflux distilling head, thermometer, magnetic stirrer, Claisen adapter, dropping funnel, and a dry ice cooled trap. 2,2′-Azobis-2-methylpropionitrile) (ABN, 0.25 g, 1.5 mmol) and 5-iodo-1-hexene[22] (10.01 g, 47.20 mmol) were added and while cooling to 0–10° with an ice bath, TBTH (14.8 g, 51.1 mmol) was added cautiously over a period of 5 min. The mixture was stirred for 4 hr while heating to 50° with an oil bath. 1-Hexene (2.75 g, 69.3%, $n^{25}D$ 1.3850) was collected in the dry ice trap at 20 mm of mercury pressure, using a water aspirator. Characteristic infrared absorption of 1-hexene at 3075, 1645, 998, and 914 cm^{-1} was observed.

Reduction of 7-Perfluorobutyl-6-iodohept-1-ene (3) with TBTH. In similar fashion 3 (6-iodo-8,8,9,9,10,10,11,11,11-nonafluoro-1-undecene, 2.43 g, 5.50 mmol) containing 4 [1-iodomethyl-2-(perfluorobutyl)methylcyclopentane, 1.99 g, 4.50 mmol], ABN (0.0328 g, 0.200 mmol), and TBTH (3.77 g, 13.0 mmol, a 1.93 *M* solution) gave 8,8,9,9,10,10,11,11,11-nonafluoro-1-undecene (**5**) and *cis*- and *trans*-1-methyl-2-(perfluorobutyl)methylcyclopentane (**6a,b**), bp 62–66° (15 mm), 2.63 g, $n^{25}D$ 1.3504 (83%). Ir showed ν_{CH} (olefinic) at 3100, $\nu_{C=C}$ at 1640 (weak), and out-of-plane bending at 992 and 910 cm^{-1}. GLC analysis (using a 6 ft × 0.125 in. column packed with 20% "Ucon Polar" LB 550-X on 60–80 mesh Gas Pack WA at 60°) showed **5**, retention time 11.2 min, 17.8% relative area, and **6** at 15.7 min, 81.5% relative area (replicate analyses). The conversion of **3** to **6** was 67.5% and of **3** to **5** was 32.5%; **5/6** then was 0.480.

Anal. Calcd for $C_{11}H_{13}F_9$: C, 41.78; H, 4.14. Found (**5/6** mixture): C, 41.77; H, 4.00.

Zinc Reduction of 7-Perfluorobutyl-6-iodohept-1-ene (3). Using a similar apparatus but with a 100-ml flask, **3** (4.86 g, 11.0 mmol) and **4** (3.98 g, 9.00 mmol), and, while stirring, powdered zinc (100 mesh, 5.0 g, 80 mmol) and glacial acetic acid (25 ml, dropwise) were added and the mixture heated to reflux temperature (62°) using an oil bath, for ¼ hr. The slurry was cooled and decanted, the zinc washed with 10 ml of ether, and the layers separated with the aid of 25 ml of saturated salt solution. Saturated sodium bicarbonate solution (25 ml) was added to the organic layer, 5 ml at a time, shaken carefully. The water layer was washed with 10 ml of ether, and the combined ether extracts dried over magnesium sulfate. Distillation gave **5** and **6a,b**, bp 66° (14 mm), 4.33 g, $n^{25}D$ 1.3517 (68.5%). A residue of 1.31 g of oil remained. GLC analysis showed **5**, 12.6% relative area, and **6a,b**, 87.5%. Ir spectra were identical for both reduction product mixtures. An NMR spectrum of the **5/6a,b** mixture gave resonances at δ 0.85, d, *J* = 7 Hz, 1.81 proton, CH_3CH of **6a**; 1.10, d, *J* = 7 Hz, 0.57 proton, CH_3CH of **6b**; 1.2–2.6, m, 10 protons, $(CH_2)_n$ and CH; 4.8–6.2, m, 0.5 proton, $CH_2{=}CH$ of **5**. Correcting for the amount of **4** originally present, the conversion of **3** to **5** was 22.9% and of **3** to **6** was 77.1%; hence, the ratio of **5/6** was 0.297.

Reduction of 8-Perfluorobutyl-7-iodooct-1-ene (7) with TBTH. **7** (7-iodo-9,9,10,10,11,11,12,12,12-nonafluoro-1-dodecene, 11.0 g, 24.1 mmol), ABN (0.0203 g, 1.25 mmol), and TBTH (9.00 g, 31.0 mmol, 1.90 *M* in the resulting solution) gave exothermic reaction at 31–43° under a nitrogen atmosphere. Distillation in a 16-in. spinning band column afforded 9,9,10,10,11,11,12,12,12-nonafluoro-1-dodecene (**8**) and *cis*- and *trans*-1-methyl-2-(perfluorobutyl)methylcyclohexane (**9**), bp 83° (13 mm), 6.41 g (81%). Tri-*n*-butyltin iodide (13.92 g) remained in the pot flask. GLC analysis (10 ft, 10% QF-1 fluorosilicone oil on Chromosorb W, at 90°) showed **8**, 98%, and **9**, 2% relative areas.

Anal. Calcd for $C_{12}H_{15}F_9$: C, 43.64; H, 4.58. Found: C, 43.81; H, 4.76.

Zinc Reduction of 8-Perfluorobutyl-7-iodooct-1-ene (7) to 8 and 9a,b. **7** (7.66 g, 16.8 mmol), zinc dust (1.57 g, 26.0 mmol), acetic acid (15 ml), and ether (15 ml) were heated to reflux for 5 hr. Distillation gave **8** and **9a,b**, bp 79–83° (14 mm), $n^{25}D$ 1.3551, 3.57 g (64%), and a liquid residue of 2.44 g. Ir showed ν_{CH}(olefinic) 3070, $\nu_{C=C}$ 1640, δ_{CH_3} 1460 and 1380 cm^{-1}, and bands at 1440, 1415, 1350, 1300, 1250–1200, 1140, 1040, 1020, 996, 918, 880, 850, and 720 cm^{-1}. An NMR spectrum showed proton resonances at δ 0.90 d, 0.28 proton, CH_3CH of **9a**; 1.2–2.6, m, 11.9 proton, $(CH_2)_n$, CH and CH_3CH of **9b**); 4.9, m, 1.75, $CH_2{=}CH$ of **8**; 5.2–6.2, m, 1.0 proton, CH= of **8**. GLC analysis (10-ft QF-1 column, 90°) gave peaks for **9a**, 14.6 min, 8.41%; **9b**, 15.8 min, 8.04%; and **9**, 18.8 min, 83.26% relative area. GLC analysis using the "Ucon Polar" column and several others failed to resolve the mixture.

Preparation of 6-Perfluorobutyl-5-iodohex-1-ene (10). 1,5-Hexadiene (16.4 g, 200 mmol), 1-iodoperfluorobutane (17.8 g, 50.0 mmol), and ABN (0.300 g, 1.82 mmol) were charged to a Fischer-Porter aerosol tube, cooled to −78°, evacuated and filled with nitrogen three times, and heated in an oil bath for 21 hr at 70.0°. Distillation in a 2-ft platinum spinning band column gave 1,5-hexadiene (11.6 g, 70.6% of the amount charged) and 5-iodo-7,7,8,8,9,9,10,10,10-nonafluoro-1-decene (**10**), bp 85° (12.0 mm), $n^{25}D$ 1.4010, 13.88 g (64.8%) in three fractions: the bis adduct,[6,21] bp 54° (0.10 mm), $n^{25}D$ 1.4350, 2.17 g, and residual oil, mostly bis adduct, 2.3 g. GLC analysis (6-ft "Ucon Polar" column, 128°) showed **10**, 98.7%, ir $\nu_{CH=CH}$ 1640 cm^{-1} and bands at 990, 920, 880, 850, 740, 730, 690, and 515 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}F_9I$: C, 28.05; H, 39.94. Found: C, 28.23; H, 2.48.

Zinc Reduction of 10. **10** (6.60 g, 15.4 mmol), acetic acid (15

ml), and diethyl ether (15 ml) were stirred while zinc dust (100 mesh, 1.57 g, 24.0 mmol) was added. Work-up and distillation gave 7,7,8,8,9,9,10,10,10-nonafluoro-1-decene (**11**), bp 39–44° (18 mm), n^{25}D 1.3374, 2.02 g (44%). Part of the volatile product was lost. A residue of 0.56 g remained. Ir showed bands similar to 8. An NMR spectrum gave proton resonances at δ 1.3–3.2, m, 8 protons, and at 4.8–6.1, m, 3 protons, in agreement with structure **11**. The R_FCH_2 group was indicated by a triplet at δ 2.75, the last of a triplet of triplets at δ 2.4; J_{HF} = 22 and J_{HH} = 7 Hz. No methyl group resonance appeared at δ 0.8–1.2. GLC analysis (6-ft "Ucon Polar" column, 62°) gave a single peak at 6.4 min.

Anal. Calcd for $C_{10}H_{11}F_9$: C, 39.75; H, 3.67. Found: C, 39.85; H, 3.80.

Zinc Reduction of 1-Perfluoropropyl-2-iodohex-1-ene (1a,b). **1a,b** (1,1,1,2,2,3,3-heptafluoro-5-iodonon-4-ene, 89.8% *E* isomer **1a** and 10.9% *Z* isomer **1b**, 10.9 g, 39.2 mmol), zinc (30 mesh, 10.0 g, 154 mmol), and ethanol (75 ml) were stirred in a flask fitted with a gas inlet tube, reflux condenser, and a paddle stirrer. Hydrogen chloride was introduced above the slurry occasionally, until gas evolution began, and the zinc began to react. The mixture was kept at 76–78° by heating as necessary. Samples taken after 1 and 2 hr both showed that very little of **1a,b** remained. The cooled liquid was decanted into 100 ml of water and extracted three times with dichloromethane (25 ml) and dried ($MgSO_4$). Distillation (16-in. spinning band column) gave (*Z*)- and (*E*)-1,1,1,2,2,3,3-heptafluoro-4-nonene (**12a,b**), bp 77° (138 mm), n^{25}D 1.3400, 5.35 g (63.2%). There was no residue. GLC analysis (10-ft QF-1 column, 85°) showed **12a** at 6.4 min, 70.6%, and **12b** at 7.2 min, 29.4%. **1a,b** was at 23.5 min retention time. Varying ratios of **12a,b** appeared in the distilled fractions. NMR gave proton resonances at δ 0.94, m, 3 protons, CH_3; 1.4, 4 protons, m, $(CH_2)_2$; 2.3, 2 protons, m, CH_2CH=; 5.0–7.0, m, 2 protons, CH=CH.

Anal. Calcd for $C_9H_{11}F_7$: C, 42.86; H, 4.40. Found: C, 42.98; H, 4.35.

Preparation of 1-Perfluoropropyl-2-iodo-1-heptene (2a,b) by Addition of 1-Iodoperfluoropropane to 1-Heptyne. 1-Iodoperfluoropropane (12.0 g, 40.0 mmol), 1-heptyne (4.80 g, 50.0 mmol), and ABN (0.0820 g, 0.500 mmol) were charged to a pressure tube and processed as for **10**. Fractionation gave **2a,b**, bp 95° (26 mm), n^{25}D 1.4135, 14.3 g (91%), in four fractions; the first three fractions contained 90.3% of **2a** and 9.67% of **2b**. The last fraction (1.9 g) contained 60.0% of **2a** and 40.0% of **2b** and was used for trapping these isomers on a GLC column (6-ft QF-1, 125°, 4-μl injections). A drop of **2a** (3.8-min retention time) on KBr plates showed ir bands: ν_{CH} 3080, 2980, 2950, 2880; $\nu_{CH=CI}$ 1640; δ_{CH} 1480, 1380, 1350; ν_{CF} 1270, 1230, 1180, 1140, 1120; bands at 1080, 975, 950, 940, 915, 820, 740, 725, 680, and 640 cm^{-1}. **2b** (5.6-min retention time) gave ir bands at $\nu_{CH=CI}$ 1640; δ_{CH} 1470, 1380, 1350; ν_{CF} same; bands at 1050, 1020, 970, 948, 915, 850, 820, 790, 740, 675, and 655 cm^{-1}. An NMR spectrum of **2a** (96%) showed proton resonances at δ 0.9, t, *J* = 5 Hz, 3 protons, CH_3; 1.4, m, 6 protons, $(CH_2)_3$; 2.68, m, 2 protons, CH_2CI=C; 6.40, t, *J* = 15 Hz, 1 proton, CF_2CH=CI.

Zinc Reduction of 1-Perfluoropropyl-2-iodo-1-heptene (2a,b). **2a,b** (1,1,1,2,2,3,3-heptafluoro-5-iodo-4-decene, 6.50 g, 16.6 mmol, 95.5% of *E* and 4.5% of *Z* isomers), zinc (30 mesh, 15.0 g in three portions, 230 mmol), ethanol (75 ml), and hydrogen chloride were employed as in the experiment with **1a,b**. Distillation afforded (*Z*)- and (*E*)-1,1,1,2,2,3,3-heptafluoro-4-decene (**13a,b**), bp 141–143° (1 atm), n^{25}D 1.3535, and bp 81° (95 mm), n^{25}D 1.3501, 3.40 g (77%). A residue of 1.2 g remained. GLC analysis (10-ft QF-1 column, 85°) gave (*Z*)-**13a** at 10.8 min, 69.3%, and (*E*)-**13b** at 12.5 min, 30.7%; **2a,b** was at 16.1-min retention time. For NMR and ir spectra see below.

Anal. Calcd for $C_{10}H_{13}F_7$: C, 45.11; H, 4.92. Found: 44.91; H, 5.09.

Preparation of 1,1,1,2,2,3,3-Heptafluoro-5-iodononane (14).[23] 1-Hexene (16.82 g, 200 mmol), 1-iodoperfluoropropane (29.6 g, 100 mmol), and ABN (0.164 g, 1.00 mmol) were charged to a pressure tube, processed as for the preparation of **10**. Distillation (2-ft platinum spinning band column) gave 1-hexene (7.55 g, 90.0 mmol), 1,1,1,2,2,3,3-heptafluoro-5-iodononane (**14**), bp 85° (23 mm), n^{25}D 1.4029, 36.1 g; and bp 73° (12 mm), n^{25}D 1.4036, 1.2 g (98%); and an oil residue (1.3 g). GLC analysis (6-ft Carbowax 1500, 20% on Chromosorb WA, 150°) gave **14** at 6.0 min, 98.14%; and an unknown at 7.6 min, 1.86%. NMR δ 0.92, m, 3 protons, CH_3; 1.12–2.2, m, 6 protons, $(CH_2)_3$; 2.82, 6 lines, 2 protons, J_{HF} = 20, J_{HH} = 7 Hz, CF_2CH_2; 4.33, 5 lines, 1 proton, *J* = 7 Hz, CH_2CHICH_2.

Preparation of (*Z*)- and (*E*)-1,1,1,2,2,3,3-Heptafluoro-4-nonene (12,a,b) by Dehydrohalogenation of 14. A solution of KOH (3.00 g, 53.5 mmol) in 60% aqueous ethanol (75 ml) was stirred by magnet bar while **14** (10.0 g, 26.4 mmol) was added and kept at 70° for 22 hr. Two layers formed which were poured into water (50 ml) and 6 *N* HCl (10 ml). The mixture was extracted into CCl_4 (three times, 10 ml) and dried ($MgSO_4$). Distillation (16-in. spinning band column) gave (*Z*)- and (*E*)-**12a,b**, bp 129°, n^{25}D 1.3392, 4.48 g, in three fractions (68%); and a residual oil (1.5 g). GLC analysis and trapping of peaks was done using a 10-ft QF-1 fluorosilicone column at 85°. (*Z*)-**12a** at 9.2 min, 27%, (*E*)-**12b** at 10.9 min, 72%, and two peaks in small amount were obtained. (*Z*)-**12a** gave ir bands at 2970, 2940, 2890, 2870; $\nu_{CH=CH}$ 1660; δ_{CH} 1470, 1350; ν_{CF} 1230, 1180, 1120; bands at 960, 670, 650, and 535 cm^{-1}. (*E*)-**12b** gave $\nu_{CH=CH}$ 1680; δ_{CH} 1465, 1350; ν_{CF} 1230, 1180, 1115; and bands at 970, 925, 735, 710, and 540 cm^{-1}.

Addition of 1-Iodoperfluoroheptane to 1-Hexadecene. Zinc Reduction of 1-Perfluoroheptyl-2-iodohexadecane (15) to 1-Perfluoroheptylhexadecane (16) and to 15,16-Bis[(perfluoroheptyl)methyl]triacontane (17). 1-Iodoperfluoroheptane (24.8 g, 50.0 mmol), 1-hexadecene (Humphrey Chemical Co, 22.4 g, 100 mmol, n^{20}D 1.4388), and ABN (0.200 g, 1.20 mmol) were heated at 80° under nitrogen for 7 hr. GLC showed only a trace of unreacted R_FI. The product (**15**) was a white solid; it was converted directly to **16** and **17**. A slurry of **15**, hexadecene (47.0 g, combined), zinc dust (65 g, 1.0 mol), magnesium powder (4.0 g, 120 mmol), and benzene (25 ml) was heated to 70° and stirred rapidly while 16% hydrochloric acid (42 ml) was added dropwise during 0.75 hr. Exothermic reaction occurred. Zinc dust (10 g), magnesium powder (1.0 g), and hydrochloric acid (43 ml) were added after 1 hr at 75°. After 3 hr, benzene (100 ml) was added, the slurry decanted and the organic layer rinsed with water twice, dried ($MgSO_4$), and distilled in a 3-ft spinning band column. 1-Hexadecene (10.6 g, 100%) was recovered, bp 87.5–90° (0.45 mm), n^{25}D 1.4390; an intermediate fraction, bp 108–127.5° (0.6 mm), n^{25}D 1.3959, 1.4 g; and 1-perfluoroheptylhexadecane (**16**), bp 122–124° (0.3 mm), 18.3 g (61.6%), a white solid. The high-boiling residue was distilled without a column, giving 15,16-bis[(perfluoroheptyl)methyl]triacontane (**17**), bp 240° (0.1 mm), 6.1 g, and bp 260° (0.1 mm), 2.2 g (total 28% of theory). The structures of **16** and of **17** were assumed to be consistent with their properties and molecular weight determination.

Anal. Calcd for $C_{23}H_{33}F_{15}$: C, 46.47; H, 5.6; F, 47.94. Found: C, 46.5; H, 5.4; F, 44.3.

Anal. Calcd for $C_{46}H_{64}F_{30}$: C, 46.5; H, 5.4; F, 47.9; mol wt, 1187. Found: C, 48.7; H, 6.0; F, 45.8; mol wt (bp in acetone) 1088, 1062.

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Registry No.—**1a**, 57325-27-6; **1b**, 57325-28-7; **2a**, 57325-29-8; **2b**, 57325-30-1; **3**, 40735-24-8; **4**, 57325-31-2; **5**, 57325-32-3; **6a**, 57325-33-4; **6b**, 57325-34-5; **7**, 13105-45-8; **8**, 57325-35-6; **9a**, 57325-36-7; **9b**, 57325-37-8; **10**, 40735-22-6; **11**, 57325-38-9; **12a**, 57325-39-0; **12b**, 57325-40-3; **13a**, 57325-41-4; **13b**, 57325-42-5; **14**, 755-48-6; **15**, 57325-43-6; **16**, 57325-44-7; **17**, 57325-45-8; 5-iodo-1-hexene, 22212-06-2; tri-*n*-butyltin hydride, 688-73-3; 1,5-hexadiene, 592-42-7; 1-iodoperfluorobutane, 423-39-2; 1-iodoperfluoropropane, 754-34-7; 1-heptyne, 628-71-7; 1-iodoperfluoroheptane, 335-58-0; 1-hexadecene, 629-73-2.

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Hydride Transfer Reduction–Rearrangements of Tricyclodecylcarbinols and Tricycloundecanols. Formation of Tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene under Phosphoric Acid Catalysis

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Hydride transfer reduction–rearrangements of 5,6-exo-trimethylene-2-norbornylcarbinol (**1**), 2- and 3-hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**2** and **3**), and 2-hydroxy-5,6-*endo*-trimethylenebicyclo[2.2.2]octane (**4x** and **4n**) in 95% sulfuric acid and excess *n*-pentane at room temperature gave 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **5**) with high selectivity (92–97%). In contrast to this, treatment of **1**, **2**, **3**, and **4** with refluxing 85% phosphoric acid–*n*-heptane resulted in the predominant formation of a novel olefin, tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene (**6**). The structure of **6** was established by an independent synthesis of the hydrogenation product (**6h**) of **6**. The olefin **6** selectively (94%) isomerized to **5** in sulfuric acid–*n*-pentane. The result suggests that tricyclo[6.2.1.$0^{2,6}$]undec-2-yl cation (**6c**) would be a key intermediate in the rearrangement sequence leading to **5**.

In the course of the identification of intermediates in adamantane rearrangement of 2,3-*exo*-tetramethylenenorbornane and 2,3-trimethylenebicyclo[2.2.2]octane, it was necessary for us to prepare an authentic specimen of 6,7-*exo*-trimethylenebicyclo[3.2.1]octane.[1] A synthesis was planned involving hydride transfer reduction–rearrangement[2–4] of 5,6-*exo*-trimethylene-2-norbornylcarbinol (**1**). This route seemed quite promising, since the isomerization of the cation (**1a**) from the carbinol **1** could give rise to the hoped-for 6,7-*exo*-trimethylenebicyclo[3.2.1]octane system, in view of the well-documented ring expansion of 2-norbornylcarbinyl to bicyclo[3.2.1]octyl cation.[5]

Sulfuric Acid Catalyzed Rearrangements of Carbinols. 5,6-*exo*-Trimethylene-2-norbornylcarbinol (**1**) was prepared from 2-*exo*-chloro-5,6-*exo*-trimethylenenorbornane[6] via Grignard reaction followed by addition to formaldehyde.[7] The carbinol thus obtained consisted of two epimers in 53:47 ratio, as shown on conventional VPC. The mixture **1** was then stirred with 95% sulfuric acid and *n*-pentane at room temperature. Samples were withdrawn at intervals from the pentane layer of the reaction mixture and examined on Golay column GC–MS, which determined the composition and established the identities of the products. Results are shown in Table I. Contrary to our expectation, no 6,7-*exo*-trimethylenebicyclo 3.2.1]octane was obtained, but 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane, **5**)[1,3,4] was found to be the main product (95%) (Scheme I).

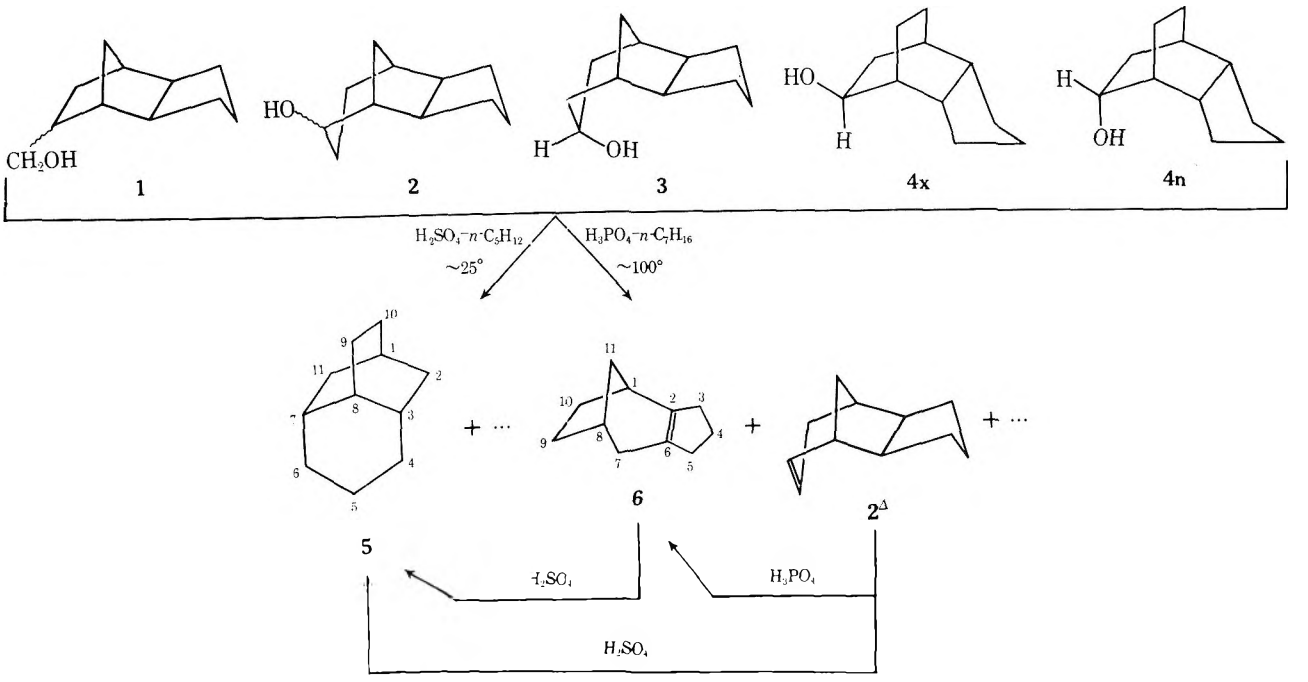
Since the first step in the rearrangement of **1** should be ring expansion to a bicyclo[3.2.1]octyl cation (**2a**),[4,5,8] reaction of 2-hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**2**) was also examined. The alcohol **2** was prepared from 5,6-*exo*-trimethylene-2-norbornene (**7**)[6] by the application of the method of Bergman[9] (dichlorocarbene ring expansion,[1] hydrolysis of allylic chlorine atom, and dechlorination–hydrogenation). The alcohol **2** thus synthesized was a mixture (89:11) of two epimers separable on conventional VPC. Reaction of **2** with sulfuric acid and *n*-pentane also gave **5** predominantly (90%) (Table I).

Table I. Sulfuric Acid Catalyzed Hydride Transfer Reduction–Rearrangement[a]

Run	Reactant	Reaction time, min	Product,[b] %[c] 15	Unknown D[d]	5	Others[e]
1	1	1	2.1	3.1	93.7	1.1
		10	2.0	2.9	94.9	0.2
		30	1.7	2.4	95.0	0.9[f]
2	2	1	1.8	2.8	89.7	5.7
		10	2.2	2.8	89.2	5.8
		30	1.8	2.7	89.0	6.5[g]
3	3	1	1.1	2.9	94.0	2.0
		15	0.8	1.3	96.8	1.1
4	4x	1	1.9	2.7	89.7	5.7[h]
		10	2.1	2.6	89.8	5.5[i]
		30	1.9	2.7	89.8	5.6[j]
5	4n	1	0.8	2.5	94.4	2.3
		10	2.0	2.4	92.1	3.5[k]
11	2Δ	30	1.1	2.2	85.0	11.7[l]
12	6	1	1.6	2.3	92.3	3.8
		5	1.4	2.1	91.7	4.5
		10	1.1	2.2	91.8	5.8[m]

[a] 100 mg of reactant, 1 g of 95% sulfuric acid, and 5 ml of *n*-pentane stirred vigorously at room temperature (~25 °C). Combined yields of pentane-soluble products were 25–35%, the balance being tarry materials. [b] Identified on Golay GC–MS by comparison with authentic specimens.[13] [c] Calculated from Golay VPC peak areas. [d] A tricycloundecane (M^+ *m/e* 150) of unknown structure detected in adamantane rearrangement of various precursors.[11,12,13] [e] Consisting of several, unidentified compounds with M^+ *m/e* 146, 148, or 150. [f] Including 0.8% 2-methyladamantane (2-Me-Ad). [g] 0.4% 2-Me-Ad. [h] 0.3% 1,2-*exo*-tetramethylenenorbornane (B_2)[13] and 1.0% 1,2-*endo*-tetramethylenenorbornane (B_3).[13] [i] 0.6% B_2, 0.4% B_3, 0.5% 2-Me-Ad, and 0.3% 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**2h**).[1] [j] 0.5% B_2, 0.5% B_3, 0.2% 2-Me-Ad, and 0.1% **2h**. [k] 1.0% 1,2-*exo*-trimethylene-*cis*-bicyclo[3.3.0]octane (B_1).[13] [l] 0.7% 2-Me-Ad and two tricycloundecadienes (M^+ *m/e* 146) in 6.2 and 1.4%, respectively. [m] 0.4% 2-Me-Ad.

Scheme I



3-*endo*-Hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**3**),[10] obtained by lithium aluminum hydride reduction of the corresponding ketone,[1] behaved similarly as its 2-hydroxy isomer (**2**) on treatment with sulfuric acid–*n*-pentane, giving **5** with 97% selectivity (Table I).

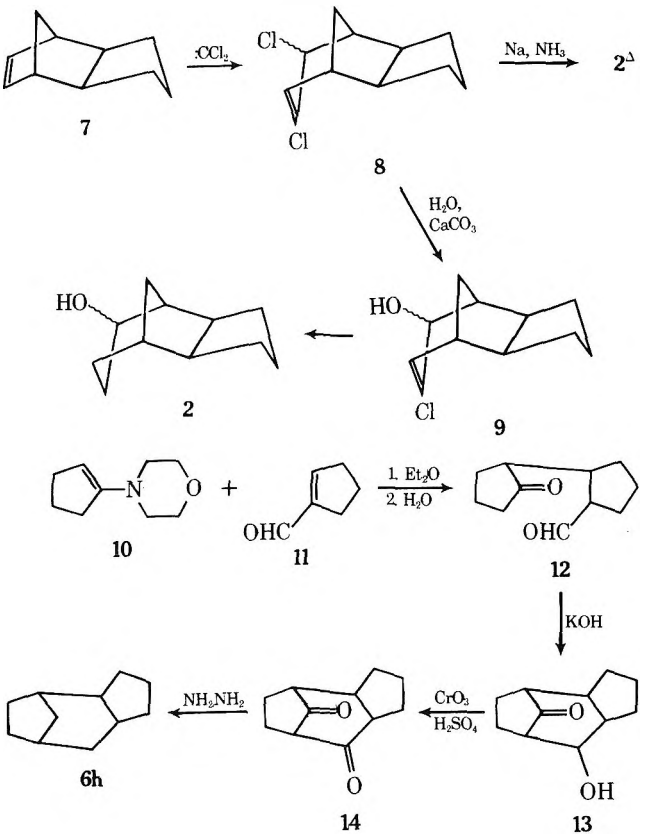
2-*exo*-Hydroxy-5,6-*endo*-trimethylenebicyclo[2.2.2]octane (**4x**), prepared by hydroboration of 5,6-*endo*-trimethylenebicyclo[2.2.2]oct-2-ene,[11] and 2-*endo*-hydroxy-5,6-*endo*-trimethylenebicyclo[2.2.2]octane (**4n**), obtained from the corresponding ketone[11] by lithium aluminum hydride reduction,[11] also gave **5** with 92–95% selectivity (Table I, Scheme I).

Phosphoric Acid Catalyzed Rearrangements of Carbinols. It has been shown in acid-catalyzed rearrangements of tricycloundecanes that product distributions varied appreciably with the kind of the catalyst used.[1,12,13] Therefore, 85% phosphoric acid in place of sulfuric acid was employed as catalyst for the hydride transfer reduction–rearrangement of the alcohols **1–4**. Since the phosphoric acid was found in preliminary experiments to catalyze the reaction quite slowly at room temperature, the reactions were run at reflux (~100 °C). It was necessary at this higher reaction temperature to change the hydride source from *n*-pentane to *n*-heptane.

Major products of the reaction under phosphoric acid catalysis were entirely different from those under sulfuric acid catalysis (Table II, Scheme I). Two tricycloundecenes, tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene (**6**) and 6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**2Δ**), consisted 70–90% of the product mixtures. The olefin **2Δ** was identified by comparison of its ir, ^{1}H NMR, and mass spectra with those of an authentic specimen prepared from 3,4-dichloro-5,6-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**8**) by dechlorination[12,14] (Scheme II).

Hydrogenation of the olefin **6** over palladium on charcoal catalyst gave two major products in 50 and 20% yields, respectively. The more abundant component was identical with an authentic 2,3-trimethylenebicyclo[3.2.1]octane (**6h**) of yet undetermined configuration, which was prepared from a cyclopentanone enamine (**10**) and 1-formylcyclopentene (**11**) by two-step condensations and the subsequent Wolff–Kishner reduction (Scheme II). The less

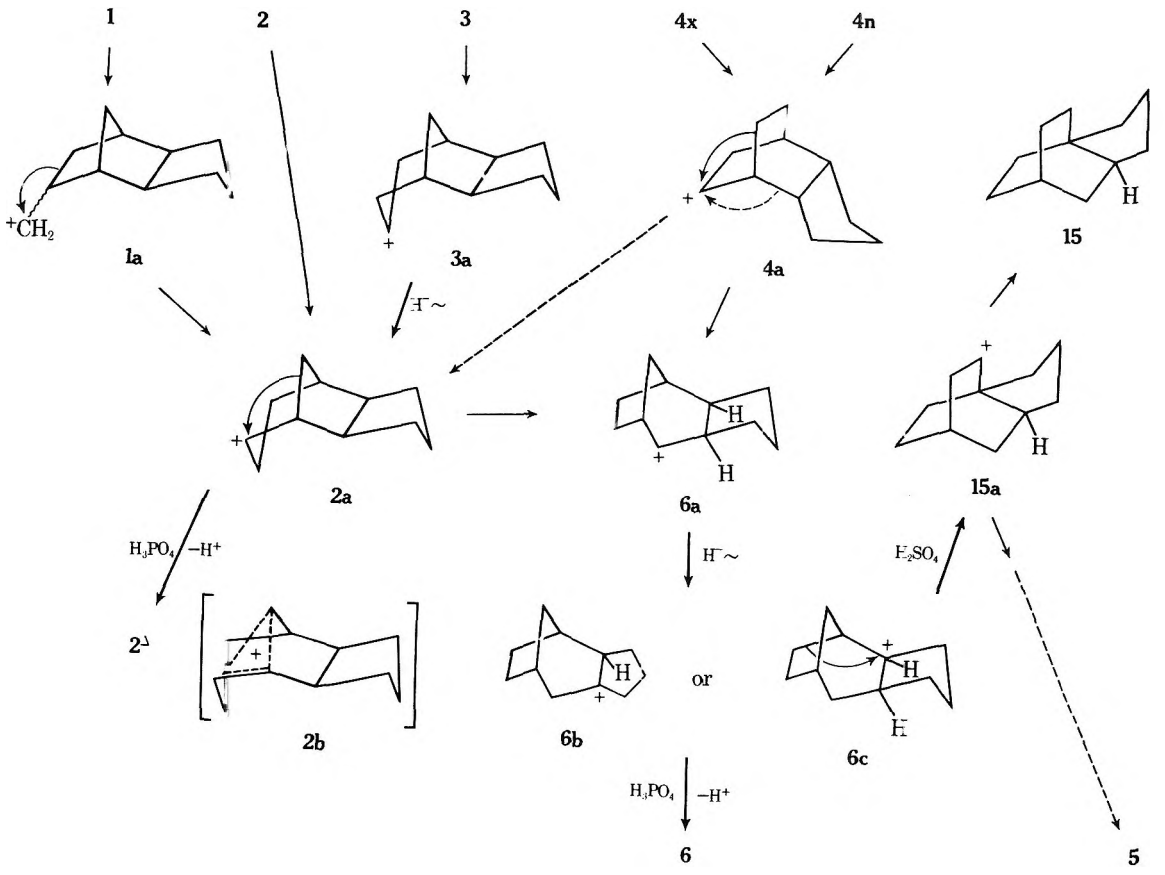
Scheme II



abundant hydrogenation product was eluted on VPC immediately after **6h** and showed an almost identical mass spectrum as that of **6h**. This suggests that **6h** and the less abundant product are configurational isomers, and an exo structure, that would presumably be more stable, might be assigned to **6h** on the basis of the abundance as well as the shorter retention time on VPC.[13]

Rearrangements of Intermediate Olefins. In the phosphoric acid catalyzed reaction of **1–4**, the ratio of the olefins **2Δ** to **6** was fairly small for the carbinol **1** (12:72), as

Scheme III



compared to those for the alcohols 2–4 (20–30:70–50). A long reaction time (7 h) required for the disappearance of 1 may have caused a secondary conversion of once formed 2^Δ into 6. This was found to be actually the case, treatment of 2^Δ with phosphoric acid for 7 h giving a 6:80 ratio of 2^Δ:6 (Table II, Scheme I).

Olefins 2^Δ and 6 formed under phosphoric acid catalysis were not found among products of sulfuric acid catalyzed reactions. An explanation for this difference in the product would be that the olefins, if ever formed at all, further isomerize to 5 and other minor products in the presence of sulfuric acid. Indeed, treatment of these olefins with sulfuric acid–*n*-pentane gave 5 selectively (85–94%) (Table I, Scheme I), as expected.

Discussion

Since all the alcohols 1–4 gave an almost identical proportion of the three main products in sulfuric acid catalyzed hydride transfer reduction–rearrangements, it would be reasonable to presume the formation of a common cationic species from these reactants. This species would most probably be 6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-yl cation (**2a**), or a symmetrical bicyclooctyl cation[5a,15] (**2b**), a nonclassical equivalent of **2a** (Scheme III). Ionization of 2 directly leads to **2a**, and any other reactant may be isomerized to **2a** in a single step by 1,2-alkyl or -hydride shift. Charge delocalization in **2a** to form a stabilized **2b** might be a driving force for these isomerizations.

The next key intermediate in the rearrangement sequence seems to be a tricyclo[6.2.1.$0^{2,6}$]undecyl cation (**6b** or **6c**, or both), which may be derived from **2a** via **6a** by 1,2-alkyl shift followed by intramolecular hydride shift. Alternatively, intramolecular hydride shift in the nonclassical cation **2b** might lead to the formation of **6b** and **6c**, thus eliminating the supposition for the existence of **6a**. Intermediacy of **6b** or **6c** would be highly probable in view of the predominant formation of the olefin **6** in phosphoric acid catalyzed reactions as well as of the isomerization of **6** to **5** in sulfuric acid with almost the same selectivity as those for the alcohols 1–4. Since phosphoric acid has been known as an effective dehydrating agent for alcohols,[16] while their isomerizations are best accomplished in sulfuric acid, the same intermediate **6b** or **6c** may give rise to diverse products according to the change in catalyst. Similarly, deprotonation in the cation **2a** (or **2b**) under the influence of phosphoric acid would lead to 6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (2^Δ).

A higher selectivity of **4n** for the formation of **6** (69%) than those of **2**, **3**, and **4x** (52, 46, and 46%, Table II) suggests that ionization of endo hydroxyl group (formation of **4a**) and migration of the exo ethano bridge (rearrange-

Table II. Phosphoric Acid Catalyzed Rearrangement[a]

Run	Reactant	Reaction time, min (h)	Product,[b] %[c] 2Δ	6	Others[d]
21[e]	1	(7)	11.5	71.8	16.7[f]
22	2	17	33.2	51.5	15.3
23	3	45	28.0	46.1	25.9[g]
24[h]	4x	25	30.6	45.5	23.9
25	4n	10	22.9	68.8	8.3[i]
31	2Δ	(7)	6.3	80.2	13.5

[a] 100 mg of reactant, 3 g of 85% phosphoric acid, and 5 ml of *n*-heptane stirred at reflux (~100°). [b] Identified on Golay GC–MS by comparison with authentic specimens. [c] Calculated from Golay VPC peak areas. [d] Consisting of several, unidentified compounds with M^+ *m/e* 146, 148, or 150. [e] Combined yield of the isolated heptane-soluble products was 66%. [f] Containing 4.6% 5. [g] Including 18.2% 5. [h] Combined yield, 80%. [i] Including 4.5% 5.

ment of **4a** to **6a**) might be concerted, probably with the participation of the ethano methylene in the ionization. This same process should be unfavorable for **4x**, in which participation of the methine to form **2a**[15,17] (as indicated by a broken arrow in **4a**) would rather be expected.

Isomerization of 2^{Δ} to **5** under sulfuric acid catalysis (run 11, Table I) occurred with a somewhat low selectivity (85%), compared to those (90–97%) in other alcohols **1–4** and olefin **6**. This result, however, does not seem to invalidate the supposition of the intermediacy of the cation **2a** (**2b**) in the rearrangement sequence, because the olefin 2^{Δ} itself would not be involved in the main pathways of the sulfuric acid catalyzed reaction. On the other hand, most of the neutral olefin 2^{Δ} may ionize in sulfuric acid to **2a** (**2b**) which enter the rearrangement reaction leading to **5**, while the remaining, small proportion could react along different pathways, that might cause the formation of a fairly large amount (7.6%) of diolefinic products (Table I, footnote *l*).

Out of a number of conceivable pathways from the cation **6b** or **6c** to **5**, the one involving 1,2-trimethylenebicyclo[2.2.2]octyl cation (**15a**) seems to be the most probable (Scheme III). Only two main intermediates, **15** and unknown D, were detected in the present rearrangement reactions (Table I). However, **15** could be considered to be the only true intermediate to **5**, since unknown D was shown[1] to be formed from and in equilibrium with **5** under sulfuric acid catalysis. In addition, **15** was demonstrated to be one of a variety of true intermediates in the trifluoromethanesulfonic acid catalyzed tricycloundecane rearrangement,[1,12,13] that would exclude the possibility of **15** being in a mechanistic dead end, as was the case for 2,4-*exo*-ethanobicyclo[3.3.1]nonane.[4] Detection of **15** as the only intermediate, in turn, may suggest that the route from **6c** to **5** should be relatively simple, possibly being a single pathway containing no competitive reaction. Thus **15a** might isomerize with appropriate hydride transfers and 1,2-alkyl shifts to 2,7-*endo*-trimethylenebicyclo[3.2.1]octyl cations and then to a cation of **5**, as imagined in our previous work.[13]

Experimental Section

All melting and boiling points are uncorrected. Instruments for the measurement of spectra and for Golay GC–MS were the same as used in the previous works,[1,12,13] except that ^{13}C NMR spectra were recorded in a Fourier transform mode at 15.03 MHz on a JEOL JNM FX-60 spectrometer. Deuteriochloroform was used as the solvent for NMR spectroscopy, and chemical shifts were reported in δ for protons and in parts per million downfield from the internal tetramethylsilane standard for ^{13}C nuclei.

5,6-*exo*-Trimethylene-2-norbornylcarbinol (**1**),[7] 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**8**),[1] 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one,[1] and 2-*exo*- and -*endo*-hydroxy-5,6-*endo*-trimethylenebicyclo[2.2.2]octane (**4x** and **4n**)[11] were prepared before.

3-Chloro-4-hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (9). A mixture of 63 g (0.29 mol) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**8**), 87 g (0.87 mol) of calcium carbonate, and 130 ml of water was heated under reflux overnight. The organic layer was separated, and the aqueous layer was extracted with two 300-ml portions of ether. The combined organic layer and ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether and fractional distillation of the residue gave 21 g (34% yield) of **9**, which solidified on standing at room temperature: bp 91–96 °C (0.15 mm); mp 49–52 °C; ir (neat) 3350 (br), 3040, 2940, 2870, 1630, 1040 (sh), 1020 cm^{-1}; ^1H NMR δ 0.9–2.8 (complex m, 12 H), 3.08 (s, 1 H, vanished on treatment with D_2O, OH), 3.85 (d, J = 5 Hz, 1 H, CHOH), 6.24 (d, J = 7 Hz, 1 H, –CH=); mass spectrum *m/e* (rel intensity) 200 (8, M^+), 198 (12, M^+), 163 (100), 145 (50), 129 (35), 95 (83), 91 (39), 85 (54), 79 (46), 77 (37), 67 (67), 41 (37).

Anal. Calcd for $C_{11}H_{15}OCl$: C, 68.4; H, 7.2; Cl, 16.8. Found C, 68.8; H, 7.5; Cl, 17.3.

2-Hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]octane (2). In an autoclave were placed 11.4 g (0.054 mol) of 3-chloro-4-hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**9**), 75 ml of tetrahydrofuran, 50 ml of 13% sodium hydroxide solution, and 6.5 g of 10% palladium on charcoal catalyst. The reaction mixture was vigorously stirred for 5 h at ambient temperature under 10 kg/cm^2 pressure of hydrogen. The catalyst was filtered off, and the filtrate was extracted with three 100-ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. The ether solution was concentrated and fractionally distilled to give 6.1 g (67% yield) of **2**, which solidified on standing at room temperature: bp 22° (0.4 mm); mp 58–60 °C; ir (neat) 3330 (br), 2940, 2860, 1470, 1450, 1020, 960 cm^{-1}; ^1H NMR δ 0.8–2.4 (complex m, 16 H), 2.71 (s, 1 H, OH), 3.86 (br s, 1 H, CHOH).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.3; H, 10.6.

The alcohol **2** thus obtained was found to consist of two isomers in 89:11 ratio, which were separable on conventional VPC. These isomers were considered to be epimers because of the similarity in their mass spectra: the major component, *m/e* (rel intensity) 166 (33, M^+), 148 (44), 120 (56), 107 (100), 81 (33), 80 (55), 79 (86), 67 (72), 44 (56), 41 (61), 39 (34); the minor component, *m/e* (rel intensity) 166 (33), 148 (42), 122 (37), 120 (56), 107 (100), 81 (44), 80 (74), 79 (96), 67 (84), 41 (72), 39 (45).

6,7-*exo*-Trimethylenebicyclo[3.2.1]oct-2-ene (2^{Δ}). Freshly cut sodium (35.4 g, 1.54 g-atom) was added in small portions to 285 ml (168 g) of liquid ammonia with efficient stirring in a period of 30 min, and the mixture was stirred for a further 20 min. A solution of 17.4 g (0.08 mol) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene (**8**) in 50 ml of ether was added dropwise to the above mixture in a period of 30 min, and the reaction was stirred for a further 1 h. Ether (200 ml) was added dropwise to the reaction mixture while ammonia was allowed to evaporate freely. Unreacted sodium and sodium amide were decomposed by the addition of 100 ml of methanol–ether (50:50), and then by 500 ml of water. The mixture was extracted with four 200-ml portions of ether. The combined ether extracts were washed with four 200-ml portions of water and dried over anhydrous calcium chloride. Evaporation of the solvent and fractional distillation of the residue gave 5.1 g (43% yield) of 2^{Δ} (91% purity, as measured on Golay GC–MS): bp 62–63 °C (5 mm); ir (neat) 3020, 2940, 2920 (sh), 2850, 2820, 1640, 1470, 1450, 1430, 780, 700, 680 cm^{-1}; ^1H NMR δ 0.8–2.7 (complex m, 14 H), 5.3 (m, 1 H), 5.9 (m, 1 H); ^{13}C NMR (multiplicity) 28.30 (t), 30.01 (t), 33.34 (t), 34.72 (t), 36.26 (t), 40.24 (d), 40.81 (d), 50.15 (d), 54.82 (d), 123.61 (d), 135.63 ppm (d); mass spectrum *m/e* (rel intensity) 148 (20, M^+), 91 (15), 80 (35), 79 (100), 78 (74), 77 (15), 67 (16), 41 (20), 39 (18), 18 (17).

Anal. Calcd for $C_{11}H_{16}$: C, 89.1; H, 10.9. Found: C, 88.7; H, 10.6.

3-*endo*-Hydroxy-6,7-*exo*-trimethylenebicyclo[3.2.1]octane (3). A solution of 2.4 g (0.0146 mol) of 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one in 10 ml of ether was dropped into a suspension of 0.56 g (0.0147 mol) of lithium aluminum hydride in 60 ml of ether under reflux, and the reaction was heated at reflux for a further 1.5 h. After unreacted metal hydride had been destroyed by the addition of ethyl acetate, the mixture was treated with methanol and then with water. Precipitates were filtered off, and the filtrate was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent left 1.6 g (66% yield) of crude **3**, which was purified on preparative VPC to give a pure sample: mp 82–83°; ir (neat) 3300 (br), 2940, 2860, 1470, 1370, 1270, 1050, 970, 800 cm^{-1}; ^1H NMR δ 0.8–2.6 (complex m, 16 H), 2.28 (s, 1 H, vanished on treatment with D_2O, OH), 3.8 (m, 1 H, CHOH); mass spectrum *m/e* (rel intensity) 148 (61), 119 (33), 107 (100), 106 (61), 94 (26), 81 (30), 80 (53), 79 (58), 78 (23), 67 (47).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.6; H, 11.2.

2-(2-Formylcyclopentyl)cyclopentanone (12). A solution of 9.0 g (0.094 mol) of 1-formylcyclopentene (**11**)[18] in 25 ml of dry ether was dropped in a period of 40 min to a stirred solution of 21.3 g (0.14 mol) of cyclopentanone morpholine enamine (**10**)[19] in 125 ml of dry ether kept at −7 °C. The reaction mixture was stirred at the same temperature for a further 2 h, and then set aside at ambient temperature overnight. The reaction mixture was mixed with 5 ml of water and stirred for 2 h. The mixture was washed with two 50-ml portions of 1% hydrochloric acid and then with water, and dried over anhydrous sodium sulfate. Ether was evaporated off from the mixture, and the residue was fractionally distilled to give 3.1 g (18% yield) of 2-(2-formylcyclopentyl)cyclopentanone (**12**): bp 107–111° (0.6 mm); ir (neat) 2950, 2860, 2700, 1730, 1710 cm^{-1}.

7-Hydroxytricyclo[6.2.1.$0^{2,6}$]undecan-11-one (13). To 50 ml of 30% potassium hydroxide solution kept at 0° was dropped with

efficient stirring a solution of 3.0 g (0.017 mol) of 2-(2-formylcyclopentyl)cyclopentanone (12) in 5 ml of ether in a period of 30 min, and the mixture was stirred overnight at ambient temperature. The organic layer was separated, and the aqueous layer was extracted with three 20-ml portions of ether. The combined organic layer and ether extracts were washed with water and dried over anhydrous sodium sulfate. Ether was evaporated, and the residue was analyzed on conventional VPC to consist of 74% 13 and 26% unreacted 12. Pure 13 was isolated by fractionation on preparative VPC: ir (neat) 3430, 2940, 2860, 1740 cm^{-1}; mass spectrum *m/e* (rel intensity) 180 (20, M^+), 162 (14), 97 (30), 84 (100), 83 (30), 67 (35), 55 (40), 41 (30), 39 (25).

Tricyclo[6.2.1.$0^{2,6}$]undeca-7,11-dione (14). To a solution of 1.6 g (0.0089 mol) of 7-hydroxytricyclo[6.2.1.$0^{2,6}$]undecan-11-one (13) in 10 ml of acetone was dropped at ambient temperature a mixture of 1.0 g (0.01 mol) of chromium trioxide, 0.9 ml of 95% sulfuric acid, and 7 ml of water in a period of 1 h, and the mixture was stirred for another 30 min. The reaction mixture was extracted with three 10-ml portions of ether, and the combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of ether gave 0.8 g (51% yield) of crude **14**: ir (neat) 2950, 2880, 1750, 1740, 1720, 1680 cm^{-1}.

Tricyclo[6.2.1.$0^{2,6}$]undecane (6h). A mixture of 0.44 g (0.0025 mol) of crude tricyclo[6.2.1.$0^{2,6}$]undeca-7,11-dione (14), 3 ml of 80% hydrazine hydrate, 2.2 g of potassium hydroxide, and 25 ml of diethylene glycol was heated under reflux for 3 h. Water and excess hydrazine hydrate were distilled off, and the residue was refluxed for a further 4 h. After addition of 100 ml of cold water, the mixture was extracted with five 20-ml portions of ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous calcium chloride. Evaporation of the ether gave 0.17 g (45% yield) of crude **6h**. Fractionation on preparative VPC gave a pure sample: ir (neat) 2950, 2870, 1470, 1450, 1350, 1320, 1310, 1250, 890, 870 cm^{-1}; ^1H NMR δ 0.8–2.4 (complex m); ^{13}C NMR (multiplicity) 24.08 (t), 27.45 (t), 27.86 (t), 31.39 (t), 32.37 (t), 33.30 (t), 33.75 (d), 34.84 (d), 37.24 (t), 37.93 (d), 47.55 ppm (d); mass spectrum *m/e* (rel intensity) 150 (66, M^+), 94 (33), 93 (51), 81 (52), 80 (98), 79 (78), 67 (100), 66 (60), 41 (73), 39 (51).

Anal. Calcd for $C_{11}H_{18}$: C, 87.9; H, 12.1. Found: C, 87.6; H, 11.8.

Tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene (6). A sample of tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene (**6**) was isolated from combined mixtures of phosphoric acid catalyzed rearrangement product on preparative VPC (retention time 15.0 min; column 0.375 in. × 10 ft, packed with 30% Carbowax 20M on Chromosorb W AW, at 144°; He pressure 1.5 kg/cm^2; injection port temperature 200 °C; detector temperature 240 °C). This sample of **6** consisted of 88.6% **6** and three tricycloundecenes of unknown structure in the amount of 9.1, 1.5, and 1.2%, respectively: ir (neat) 3050 (sh), 2940, 2860, 1660 (w), 1450, 1290, 1050, 940 cm^{-1}; ^1H NMR δ 0.8–3.0 (complex m); ^{13}C NMR (multiplicity, rel intensity) 22.54 (t, 1), 30.74 (t, 1), 33.75 (d, 1), 34.60 (t, 2), 35.37 (t, 1), 36.30 (d, 1), 36.71 (t, 1), 37.12 (t, 1), 130.11 (s, 1), 142.29 ppm (s, 1).

Anal. Calcd for $C_{11}H_{16}$: C, 89.1; H, 10.9. Found: C, 88.9; H, 11.0.

The mass spectrum of **6** was taken in the Golay GC–MS instrument: *m/e* (rel intensity) 148 (35 M^+), 120 (23), 119 (100), 105 (14), 92 (18), 91 (72), 80 (15), 79 (32), 77 (16), 66 (14), 53 (8), 51 (8), 41 (20), 39 (19).

Hydrogenation of Tricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene (6). A sample of **6** (0.43 g, 0.0029 mol) isolated in the preceding paragraph was mixed with 0.11 g of a 5% palladium on charcoal catalyst and 15 ml of ethyl acetate, and hydrogenated at 120° under 50 kg/cm^2 of hydrogen for 18 h. The catalyst was filtered off, and the filtrate was concentrated to give 0.42 g (96% yield) of the residue. This residue was analyzed on Golay GC–MS to contain four major components in the amount of 1.9, 11.0, 51.6, and 21.3%, as listed in the order of increasing retention time. The three, early eluted components were identified as unreacted **6**, 1,2-trimethylenebicyclo[2.2.2]octane (**15**), and tricyclo[6.2.1.$0^{2,6}$]undecane (**6h**), respectively, by comparison of their retention times and mass spectra with those of authentic specimens.

The last eluted component was of unknown structure, and had a mass spectrum *m/e* 150 (84, M^+), 122 (69), 121 (100), 93 (60), 80 (82), 79 (88), 67 (99), 66 (54), 41 (77), 39 (49). This mass spectrum was almost identical with that of **6h**, except that two peaks with *m/e* 122 and 121 were of low intensity in the spectrum of **6h**.

Hydride Transfer Reduction–Rearrangement under Sulfuric and Phosphoric Acid Catalysis. A reactant (0.1 g) dissolved in 5 ml of *n*-pentane was mixed with 1 g of 95% sulfuric acid, and the mixture was stirred vigorously at room temperature. Samples were withdrawn from the pentane layer of the reaction mixture while stirring was interrupted, and examined on Golay GC–MS. After the reaction was completed, the pentane layer was separated, washed with water, and dried over anhydrous sodium sulfate. Pentane was evaporated off from the solution, and the residue was weighed to calculate yields. The ratio of reactants to pentane and sulfuric acid was the same for preparative as for analytical runs.

In phosphoric acid catalyzed rearrangement reactions, 5 ml of *n*-heptane and 3 g of 85% phosphoric acid were used for 0.1 g of a reactant. Reactions were run at reflux. Analysis and treatment of the reaction mixture were the same as for sulfuric acid catalyzed reactions.

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Registry No.—1, 57526-50-8; **2** *exo*-OH, 57496-69-2; **2** *endo*-OH, 57526-51-9; **2A**, 57526-52-0; **3**, 57526-98-4; **4n**, 56846-34-5; **4x**, 56804-83-2; **6**, 57496-70-5; **6h**, 51027-86-2; **8**, 53432-47-6; **9**, 57496-71-6; **10**, 936-52-7; **11**, 6140-65-4; **12**, 57496-72-7; **13**, 57496-73-8; **14**, 57496-74-9; 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one, 53432-46-5; sulfuric acid, 7664-93-9; phosphoric acid, 7664-38-2.

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Transmission of Substituent Effects. Correlation of Methyl to Hydrogen Rate Ratios in Diverse Heterocyclic Systems with CNDO/2 Parameters[1a]

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A modification of the Dewar–Grisdale equation, parameterized with Brown's electrophilic substituent constants, σ^+, and CNDO/2 regional charge distributions, is successful in correlating reactivity ratios for the solvolysis of a wide variety of heteroarylethanol derivatives and nuclear substituted analogues. The equation $\log k_{Me}/k_H = 1.41\rho\Delta q_{ij}$, predicted by this development, is closely obeyed by the observed reactivity ratios for 34 pairs of compounds.

Recent reports from this laboratory have explored the possibilities for correlating the reactivity of a variety of heterocyclic systems with simple benzene derivatives. We have successfully applied a modification of the Dewar–Grisdale equation[2] to benzofuran,[3,4] furan,[5] thiophene,[6] and benzothiophene[7] systems. We examined substituent effects on the rates of solvolysis of heteroarylmethyl derivatives; generally excellent correlations resulted.

It is the purpose of the present report to extend these observations and, in particular, to explore a further consequence of the earlier derivations: namely, that the methyl group, as a substituent, will exert its influence almost entirely through its ability to stabilize an electron-deficient species (carbonium ion).

The modified Dewar–Grisdale equation developed by Noyce and Nichols is given in eq 1.[3,6]

$$(\sigma_{ij}^+) = \frac{F_x^+}{r_{ij}} + M_x^+\Delta q_{ij} \quad (1)$$

Here, $(\sigma_{ij}^+)_x$ is the substituent constant for any substituent X; r_{ij} is the distance (in benzene bond lengths) between the reaction center located at ring position j and the substituent at position i; Δq_{ij} is the regional charge developed at the point of substitution as determined from CNDO/2 calculations (see below). F_x^+ and M_x^+, the field and resonance capabilities of substituent X, are determined by substituting into eq 1 the σ_p^+ and σ_m^+ values from the benzene series[8] and their associated r_{ij} and Δq_{ij} values generated by CNDO/2 calculations and solving the resulting pair of simultaneous equations. In this manner *unique* values of F_x^+ and M_x^+ for each substituent are obtained. This procedure removes the necessity for considering any set of special σ values for substituents on heterocyclic rings. The possibilities for extension to other aromatic systems are obvious.

Regional charges are determined by molecular orbital calculations for the transformation $ArCH_3 \rightarrow ArCH_2^+$. The methyl and methylene groups located at position j represent a model for the starting state and the transition state along the reaction coordinate of the limiting solvolysis reaction. The regional charges are determined from the differences between the gross atomic populations at position i in $ArCH_3$ and $ArCH_2^+$. Since Ar can be any aromatic or heteroaromatic nucleus, regional charges at many positions for a large number of aromatic systems may be determined.

The effective response to the introduction of a substituent at any position may then be predicted. For the methyl group as a substituent, F^+ is determined to be -0.028 and M^+ is determined to be -1.41. Insertion of these values into eq 1 yields eq 2.

$$(\sigma_{ij}^+)_{CH_3} = \frac{-0.028}{r_{ij}} - 1.41\Delta q_{ij} \quad (2)$$

Inasmuch as the field component (F^+) for the methyl group is quite small,[9] and r_{ij} is always greater than 1.0, the resonance component (M^+) dominates and eq 2 can be approximated by eq 3.

$$(\sigma_{ij}^+)_{CH_3} = -1.41\Delta q_{ij} \quad (3)$$

Thus the modified Hammett equation, eq 4, can be written for the correlation of the methyl substituent effect in a variety of systems.

$$\log \frac{k(CH_3)}{k(H)} = \rho(\sigma_{ij}^+)_{CH_3} \quad (4)$$

or

$$\log \frac{k(CH_3)}{k(H)} \cong -1.41\rho\Delta q_{ij} \quad (5)$$

Inspection of eq 5 reveals that the solvolytic rate enhancement observed upon methyl substitution in the aromatic nucleus should be directly predictable from the regional charge developed at the point of substitution. Data with which to test this hypothesis are available from a wide range of aromatic systems (see Table I), including data from previous studies from this laboratory. The plots shown in Figures 1 and 2 show the quality of the linear correlation of methyl rate enhancement and regional charge predicted by eq 5.

We have combined data from several sources to generate the results presented in Table I. It is well known that ρ is temperature sensitive; for solvolysis reactions it decreases in magnitude with increasing temperature. Hence, the data are presented in two groups, at 25° or at 75°.

On the other hand, the value of ρ for the solvolysis of 1-phenylethanol derivatives shows very little sensitivity to the leaving group, be it *p*-nitrobenzoate ion, chloride, or tosylate. The value of ρ is also relatively insensitive to modest changes in solvent for these systems. Thus we have combined data for *p*-nitrobenzoate solvolysis for the most reactive aromatic substrates, with data for chlorides, and even for tosylates, involving the least reactive aromatic substrates.

A number of the individual cases reported in Table I merit additional comment. The solvolysis of the 5-methyl analogue of 1-(3-thienyl)ethyl *p*-nitrobenzoate (entry 20) shows a relatively large rate acceleration for introduction of a methyl group at a nonconjugating position (compare benzene, entries 3, 8, and 21). This magnitude of acceleration is predicted by the value of Δq. Such an effect is also observed with the furan system (entries 18 and 19). Most striking is the result for imidazole (entry 16). Again the magnitude of the acceleration is in line with the value of Δq.

Table I. Methyl Rate Enhancements and Regional Charges for 1-Aryl-1-ethyl Systems[a]

Entry	Compd	Leaving group[a]	i[b]	j[c]	$k(CH_3)/k(H)$	Δq_{ij}	Ref
			25°C				
1	Furan	OPNB	5	2	212	0.2763	10
2	Thiophene	OPNB	5	2	81	0.2051	6
3	Benzene	Cl	3	1	2.20	0.0368	e
4	Benzene	Cl	4	1	58.0	0.2115	e
5	Thiazole	OPNB	2	5	45.5	0.2030	11
6	Thiazole	OPNB	5	2	89.5	0.2268	11
7	Toluene	Cl	5	2	45.5	0.2028	e
8	Toluene	Cl	4	2	2.00	0.0337	e
9	Benzothiazole	OTs	4	2	4.47	0.1036	e
10	Benzothiazole	OTs	5	2	2.80	0.0371	e
11	Benzothiazole	OTs	6	2	10.09	0.1238	e
12	Benzimidazole	Cl	5	2	8.15	0.0600	e
13	Benzimidazole	Cl	5, 6	2	82.8	0.1880[d]	e
14	Pyrazole	Cl	3	5	3.74	0.0479	e
15	Imidazole	OPNB	5	2	59.7	0.2396	12
16	Imidazole	OPNB	4	2	20.3	0.1111	12
17	Imidazole	OPNB	4, 5	2	1013	0.3507[d]	12
			75°C				
18	Furan	OPNB	5	3	8.85	0.1076	5
19	2-Methylfuran	OPNB	5	3	7.53	0.1166	e
20	Thiophene	OPNB	5	3	3.92	0.0735	e
21	Benzene	Cl	3	1	2.02	0.0368	e
22	Benzene	OPNB	4	1	58.00	0.2115	e
23	Benzo[*b*]thiophene	OPNB	5	2	2.57	0.0398	7
24	Benzo[*b*]thiophene	OPNB	6	2	9.00	0.1246	7
25	Benzo[*b*]thiophene	OPNB	7	2	1.59	0.0323	7
26	Benzo[*b*]furan	OPNB	5	2	2.78	0.0473	4
27	Benzo[*b*]furan	OPNB	6	2	11.70	0.1377	4

[a] Solvent, 80% ethanol; Cl = chloride, OPNB = *p*-nitrobenzoate, OTs = tosylate. [b] i = position of methyl substitution. [c] j = position of 1-ethyl side chain. [c] Assuming additivity. [e] Present study. [f] $k(C_2H_5)/k$ (H).

The slope of the line in Figure 1, for secondary systems at 25°C, is 7.9 (correlation coefficient $r = 0.973$). This compares favorably with the slope of 8.6 predicted by eq 5 (-1.41×-6.1). At 75°C the observed slope (Figure 2) of 8.0 ($r = 0.992$) compares equally favorably with a predicted value of 7.8. The results seem eminently satisfactory, considering the very wide diversity of compound types brought together for this correlation.

There are also appreciable data available on tertiary systems, and this information is collected in Table II. The naphthalene case (33) is instructive; treating the data of Baliah and Nadar[14] in this fashion is particularly satisfy-

Table II. Methyl Rate Enhancements and Regional Charges for 2-Aryl-2-propyl Systems at 25°C

Entry	Compd	Leaving group[a]	i[b]	j[c]	$k(CH_3)/k(H)$	Δq_{ij}	Ref
28	Pyridine[d]	Cl	2	4	1.85	0.0286	13
29	Pyridine[d]	Cl	2	5	19.00	0.2212	13
30	Pyridine[d]	Cl	3	5	1.96	0.0441	13
31	Benzene[e]	Cl	3	1	2.00	0.0368	8
32	Benzene[e]	Cl	4	1	26.00	0.2115	8
33	Naphthalene[f]	Cl	6	2	6.10	0.1232	14
34	Furan[d]	OPNB	5	3	6.00	0.1076	5

[a] Cl = chloride; OPNB = *p*-nitrobenzoate. [b] i = position of methyl substitution. [c] j = position of 2-propyl side chain. [d] Solvent, 80% ethanol. [e] Solvent, 90% acetone. [f] Solvent, 95% acetone, 30°C.

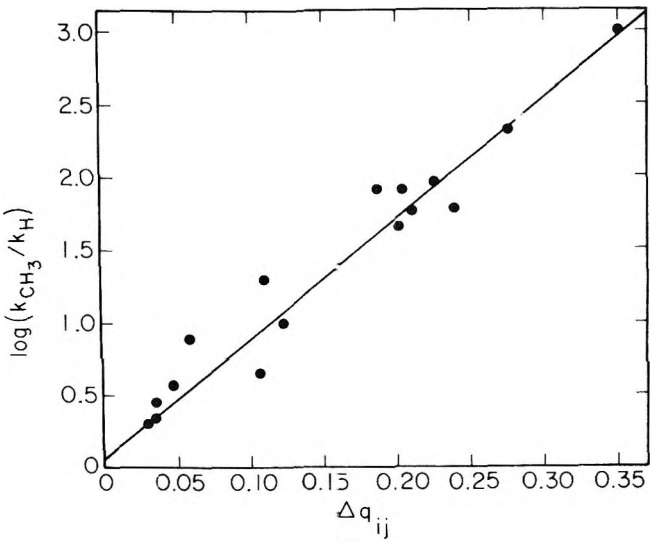

Figure 1. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of 1-arylethanol derivatives in 80% ethanol at 25° ($r = 0.973$).

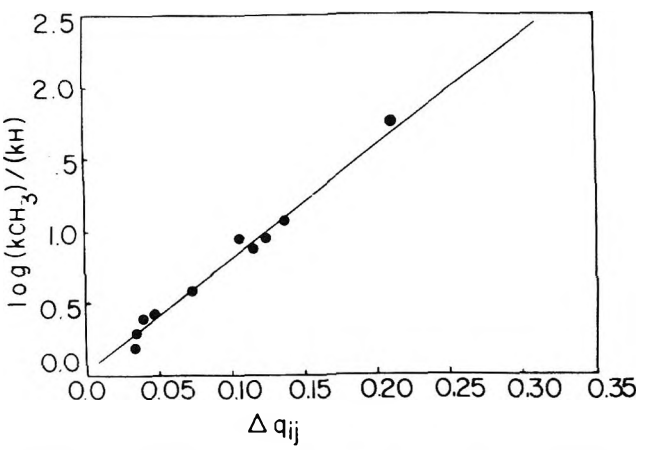

Figure 2. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of 1-arylethanol derivatives in 80% ethanol at 75° ($r = 0.992$).

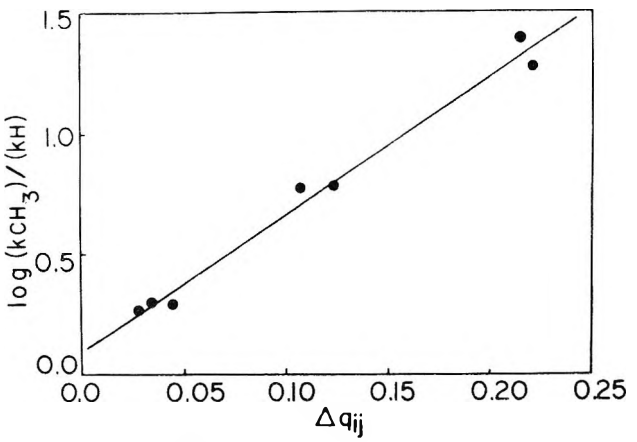

Figure 3. Log $[k(CH_3)/k(H)]$ vs. Δq_{ij} for solvolysis of tertiary systems at 25° (r = 0.990).

ing, as it immediately explains their "unexpected" difficulty with high reactivity for 6-methoxy-2-naphthyl-2-chloropropane. The results for the tertiary systems are presented graphically in Figure 3. The observed slope, 5.8 (r = 0.990) is to be compared with the predicted slope of 6.3 [ρ = −4.5 (from Brown's studies) × −1.41].

Since ρ incorporates influences such as variation of solvent, temperature, and reaction center (primary, secondary, or tertiary) on the magnitude of the response to the influence of the substituent, eq 5 can be reorganized to give eq 6.

$$\frac{1}{\rho}\log\frac{k(CH_3)}{k(H)} = -1.41\,\Delta q_{ij} \qquad (6)$$

Equation 6 permits all of the data presented above to be correlated by a single function. When the data are treated together in this fashion, the best slope of the line is −1.33, which is in excellent agreement with the theoretical slope of −1.41.

The correlations presented in Figures 1–3 support the assumption introduced in eq 3, that the resonance capability of the methyl group is the predominant component of the methyl substituent effect. Furthermore, the use of regional charges to obtain a quantitative picture of charge delocalization in the solvolysis transition state is supported by these correlations.

The relationship between methyl rate enhancement and regional charge seen in eq 6 is not solely applicable to the limiting solvolysis of substituted heteroarylcarbinyl systems. With suitable transition state models, which are necessary for the calculation of regional charges, methyl rate enhancements observed for other reactions, e.g., electrophilic bromination, should also be successfully predicted by eq 5. In a reverse manner, the methyl group might be used as a sensitive probe for charge delocalization in the transition states of many organic reactions.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected as are boiling points. Proton magnetic resonance spectra were obtained on a Varian T-60 instrument with tetramethylsilane as the internal standard. Chemical shifts are given in parts per million downfield from Me_4Si (δ values), and the following legend is used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; and b, broad. All elemental analyses were performed by the Analytical Services Laboratory, College of Chemistry, University of California, Berkeley.

Kinetic rate constants were evaluated from the raw experimental titers by the LSKIN 1 program.[15]

1-(2-Methylphenyl)ethyl chloride[16] **(1)** was prepared, using thionyl chloride with the alcohol, which was from o-methylbenzaldehyde and methylmagnesium bromide. **1-(2,4-Dimethylphenyl)ethyl chloride**[16] **(2)** was prepared from the corresponding alcohol[16] using thionyl chloride. **1-(2-,5-Dimethylphenyl)ethyl chloride (3)** was prepared from 1-(2,5-dimethylphenyl)ethanol,[17] using thionyl chloride in dichloromethane.

1-(2-Methyl-3-furyl)ethyl *p*-Nitrobenzoate (4). 2-Methyl-3-acetylfuran[18] was reduced with sodium borohydride in anhydrous methanol, and the 1-(2-methyl-3-furyl)ethanol was obtained in 91% yield: bp 38–40° (0.3 mm); NMR ($CDCl_3$) δ 1.33 [d, 3, J = 6 Hz, $-CH(CH_3)_2$], 1.87 (s, 3, 2-CH_3), 3.63 (broad singlet, 1, –OH), 4.67 [q, 1, J = 6 Hz, $-CH(OH)CH_3$], 6.23 (d, 1, J = 2 Hz, 4-H), 7.13 (d, 1, J = 2 Hz, 5-H).

The alcohol was converted directly to the p-nitrobenzoate, using p-nitrobenzoyl chloride in pyridine. 1-(2-Methyl-3-furyl)ethyl p-nitrobenzoate was purified by crystallization from mixed hexanes: mp 84–85°; yield 61%; NMR (CCl_4) δ 1.62 [d, 3, J = 6 Hz, $-CH(OPNB)CH_3$], 2.35 (s, 3, 2-CH_3), 6.05 [q, 1, J = 6 Hz, $-CH(OPNB)CH_3$], 6.32 (d, 1, J = 2 Hz, 4-H), 7.15 (d, 1, J = 2 Hz, 5-H), 8.12 (s, 4, ArH).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.11; H, 4.93; N, 4.98.

1-(2,5-Dimethyl-3-furyl)ethyl *p*-Nitrobenzoate (5). Reduction of 2,5-dimethyl-3-acetylfuran[19] with sodium borohydride in methanol afforded 1-(2,5-dimethyl-3-furyl)ethanol, NMR (CCl_4) δ 1.22 (d, 3, J = 6 Hz, $>CHCH_3$), 2.13 (s, 6, 2-CH_3 and 5-CH_3), 3.52 (broad, 1, OH), 4.45 (q, 1, J = 6 Hz $>CHCH_3$), 5.70 (s, 1, 4-H), which was converted directly to the p-nitrobenzoate using p-nitrobenzoyl chloride and pyridine. The crude ester **5** was purified by recrystallization from mixed hexanes: mp 79–80°; NMR (CCl_4) δ 1.58 [d, 3, J = 6 Hz, $-CH(OPNB)CH_3$], 2.20 and 2.28 (two singlets, 6, 2-CH_3 and 5-CH_3), 5.88 (s, 1, 4-H), 5.93 [q, 1, J = 6 Hz, $-CH(OPNB)CH_3$], 8.08 (s, 4, C_6H_4).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.52; H, 5.20; N, 4.72.

1-(3-Thienyl)ethyl *p*-Nitrobenzoate (6) was prepared as previously reported.[20]

1-(5-Methyl-3-thienyl)ethanol. 4-Bromo-2-methylthiophene, prepared by the method of Gol'dfarb, Vol'kenshtein, and Lopatin[21] (22 g), was dissolved in 100 ml of dry ether and added dropwise to a solution of n-butyllithium ether (90 ml of 15%) under nitrogen at −78°. The reaction mixture was stirred for 1 h. Acetaldehyde (17.0 ml, 13.2 g, 0.30 mol) in 50 ml of ether was added. The mixture was stirred for another 1 h and then removed from the dry ice bath and quenched with 100 ml of water. The ether layer was separated and the aqueous phase was washed with 3 × 50 ml of ether. The combined ether layers were dried (Na_2CO_3) and filtered, and the ether was removed on the rotary evaporator. The residue was distilled to yield 1-(5-methyl-3-thienyl)ethanol: 6.0 g (34%); bp 65–66° (0.03 mm); NMR (CCl_4) δ 1.32 [d, 3, J = 6 Hz, $-CH(OH)CH_3$], 2.38 (s, 3, 5-CH_3), 6.52 (broad doublet, 1, 4-H, coupled to 5-CH_3 with J < 1 Hz), 6.63 (d, 1, J < 1 Hz, 2-H).

Anal. Calcd for $H_7H_{10}OS$: C, 59.11; H, 7.09; S, 22.55. Found: C, 58.96; H, 7.09; S, 22.36.

1-(5-Methyl-3-thienyl)ethyl *p*-Nitrobenzoate (7). The alcohol was treated with freshly recrystallized p-nitrobenzoyl chloride in dichloroethane solution to which triethylamine had been added. The crude product was crystallized from mixed hexanes to yield ester **7**: mp 45.5–47°; NMR (CCl_4) δ 1.65 [d, 3, J = 6 Hz, $CH(OPNB)CH_3$], 2.45 (bs, 5-CH_3), 6.03 [q, 1, J = 6 Hz, $CH(OPNB)CH_3$], 6.62–6.75 (m, 1, 4-H, coupled to 5-CH_3 and 2-H), 6.92 (d, 1, J < 1 Hz, 2-H), 8.07 (s, 4, C_6H_4).

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.67; H, 4.39; N, 4.90; S, 10.92.

1-(2-Benzothiazolyl)ethanol was prepared from benzothiazole by metalation with butyllithium and addition of acetaldehyde to the lithio derivative. Work-up and distillation gave a viscous liquid, bp 112–116° (0.4 mm), which slowly solidified at room temperature (12.2 g, 68%). The solid was recrystallized from hexane–ether to give white needles: mp 62–63.5° (lit.[22] 68°); NMR (CCl_4) δ 1.62 (d, 3, $-CHCH_3$, J = 7 Hz), 4.33 (s, 1, –OH), 5.13 (s, 1, $-CHCH_3$, J = 6.5 Hz), 7.15–7.44 (m, 2, 5-H and 6-H), and 7.64–7.90 (m, 2, 4-H and 7-H).

Anal. Calcd for C_9H_9NOS: C, 60.34; H, 5.03; N, 7.82; S, 17.88. Found: C, 60.25; H, 4.98; N, 7.64; S, 18.02.

1-(2-Benzothiazolyl)ethyl Tosylate (8). A solution of 1-(2-benzothiazolyl)ethanol (5.00 g) and triethylamine (2.82 g) was prepared in 10 ml of 1,2-dichloroethane. Recrystallized p-toluenesulfonyl chloride (5.32 g) dissolved in 15 ml of 1,2-dichloroethane was added in portions to the alcohol–amine solution. The resulting solution was stirred for 1 h at room temperature. The mixture was refrigerated for 24 h, after which time it was warmed to room temperature and filtered. The triethylammonium chloride precipitate

was washed with fresh solvent, and the combined organic portions were concentrated under vacuum. The orange oil thus obtained was taken up in several portions of boiling hexane (ca. 800 ml total), and the combined hexane extracts were set aside to crystallize. Filtration afforded 8 as a fine white solid (4.7 g, 51%): mp 59–60°; NMR (CCl_4) δ 1.77 (d, 3, $-CHCH_3$, J = 6 Hz), 2.35 (s, 3, $ArCH_3$), 5.77 (q, 1, $-CHCH_3$, J = 6.5 Hz), 7.06–7.35 (m, 4, 5-H and 6-H and *m*-ArH), and 7.61–7.89 (m, 4, 4-H and 7-H and *o*-ArH).

Anal. Calcd for $C_{16}H_{15}NO_3S_2$: C, 57.66; H, 4.50; N, 4.20; S, 19.22. Found: C, 57.59; H, 4.51; N, 4.31; S, 19.32.

6-Methylbenzothiazole. 6-Methylbenzothiazole-2-carboxylic acid, mp 108–110° (7.3 g),[23] was decarboxylated by steam distillation. The steam distillates were extracted with chloroform and dried ($MgSO_4$). Removal of solvent gave a yellow oil (5.2 g), which was distilled to give a colorless liquid (4.6 g, 81%): bp 81–82° (1.4 mm) [lit.[24] 118–120° (1.3 mm)]; NMR (CCl_4) δ 2.36 (s, 3, 6-CH_3), 7.15 (dd, 1, 5-H), 7.47–7.54 (m, 1, 7-H), 7.93 (d, 1, 4-H, J = 8 Hz), and 8.77 (s, 1, 2-H).

Anal. Calcd for C_8H_7NS: C, 64.43; H, 4.70; N, 9.40; S, 21.48. Found: C, 64.21; H, 4.67; N, 9.49; S, 21.34.

1-(6-Methyl-2-benzothiazolyl)ethanol was prepared by metalation of 6-methylbenzothiazole with butyllithium at −78° and subsequent addition of acetaldehyde. The isolated product was crystallized from hexane to afford white crystals (50%): mp 108.5–110.5°; NMR ($CDCl_3$) δ 1.68 (d, 3, $-CHCH_3$, J = 6 Hz), 2.47 (s, 3, 6-CH_3), 5.18 (q, 1, $-CHCH_3$, J = 6.5 Hz), 7.15–7.31 (m, 1, 5-H), and 7.65–7.89 (m, 2, 4-H and 7-H).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 62.05; H, 5.88; N, 7.03; S, 16.62.

1-(6-Methyl-2-benzothiazolyl)ethyl tosylate (9) was prepared from the alcohol as above. The crude material isolated was found by NMR to be a mixture of alcohol (30%) and tosylate **9** (70%). Further purification was extremely tedious. Hence, this mixture was used in kinetic runs without further purification: NMR (CCl_4) δ 1.75 (d, 3, $-CHCH_3$, J = 6 Hz), 2.45 (s, 3, $ArCH_3$), 5.78 (q, 1, $-CHCH_3$, J = 6 Hz), 7.11–7.24 (m, 3, *m*-ArH and 5-H), and 7.54–7.80 (m, 4, *o*-ArH and 4-H and 7-H).

1-(5-Methyl-2-benzothiazolyl)ethanol. Metalation of 5.6 g of 5-methylbenzothiazole[25] with butyllithium at −78° was followed by addition of acetaldehyde (3.31 g). The dry ice bath was then removed and stirring was continued for 15 min. The yellow mixture was poured into saturated ammonium chloride (200 ml), and the resulting solution was extracted with ether. After drying ($MgSO_4$) and removing solvent, a golden oil was obtained, which was distilled to give a light yellow solid (6.0 g), bp 124–127° (0.05 mm). Recrystallization from hexane gave white needles (4.0 g, 55%): mp 83–85°; NMR ($CDCl_3$ and CCl_4 mixture) δ 1.60 (d, 3, $-CHCH_3$, J = 6 Hz), 2.38 (s, 3, 5-CH_3), 4.83 (b, 1, –OH), 5.10 (q, 1, $-CHCH_3$, J = 6 Hz), 6.98 (bd, 1, 6-H), 7.50 (bs, 1, 4-H), and 7.51 (d, 1, 7-H, J = 8 Hz).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 61.99; H, 5.55; N, 7.12; S, 16.45.

1-(5-Methyl-2-benzothiazolyl ethyl tosylate (10) was prepared in the usual fashion. The crude product was crystallized from hexane to give fine white needles (75%): mp 116–117°; NMR (CCl_4) δ 1.78 (d, 3, $-CHCH_3$, J = 6 Hz), 2.36 (s, 3, $ArCH_3$), 2.47 (s, 3, 5-CH_3), 5.78 (q, 1, $-CHCH_3$, J = 6 Hz), 7.00–7.24 (m, 3, 6-H and *m*-ArH), and 7.51–7.81 (m, 4, 4-H and 7-H and o-ArH).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.79; H, 4.90; N, 4.03; S, 18.44. Found: C, 58.72; H, 4.82; N, 4.17; S, 18.32.

1-(4-Methyl-2-benzothiazolyl)ethanol. Decarboxylation of 4-methylbenzothiazole-2-carboxylic acid[23] gave 4-methylbenzothiazole.[25] Metalation with butyllithium and subsequent addition of acetaldehyde gave 1-(4-methyl-2-benzothiazolyl)ethanol in 73% yield: mp 65–68° (white crystals from hexane); NMR (CCl_4) δ 1.60 (d, 3, $-CHCH_3$, J = 6 Hz), 2.62 (s, 3, 4-CH_3), 4.12 (b, 1, –OH), 5.09 (q, 1, $-CHCH_3$, J = 6 Hz), 6.97–7.21 (m, 2, 5-H and 6-H), and 7.34–7.54 (m, 1, 7-H).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.18; H, 5.70; N, 7.25; S, 16.58. Found: C, 62.37; H, 5.68; N, 7.14; S, 16.74.

1-(4-Methyl-2-benzothiazolyl)ethyl tosylate (11) was prepared in the usual fashion. Crystallization of crude **11** from hexane was induced by chilling in dry ice and scratching, which produced a fine white solid: mp 74–75°; NMR (CCl_4) δ 1.77 (d, 3, $-CHCH_3$, J = 7 Hz), 2.34 (s, 3, $ArCH_3$), 2.60 (s, 3, 4-CH_3), 5.80 (q, 1, $-CHCH_3$, J = 6 Hz), 7.03–7.22 (m, 4, 5-H and 6-H and *m*-ArH), and 7.44–7.75 (m, 3, 7-H and *o*-ArH).

Anal. Calcd for $C_{17}H_{17}NO_3S_2$: C, 58.79; H, 4.90; N, 4.03; S, 18.44. Found: C, 58.77; H, 5.05; N, 4.22; S, 18.62.

1-(1-Methyl-2-benzimidazolyl)ethyl Chloride (12). This preparation followed the procedure of Skolnick, Miller, and Day.[26]

1-(1,5-Dimethyl-2-benzimidazolyl)ethanol. This procedure followed the sequence used by Beaven et al.[27] The *N*-methyl-2-amino-4-methylaniline was treated with lactic acid by the Phillips method[28] to give the title compound, mp 94–95°, NMR ($CDCl_3$) δ 1.65 (d, 3, $-CHCH_3$), 2.45 (s, 3, 5-CH_3), 3.70 (s, 3, NCH_3), 3.95 (bs, 1, OH), 5.10 (q, 1, $CHCH_3$), 7.20 (m, 3, ArH), which was converted directly to the chloride.

1-(1,5-Dimethyl-2-benzimidazolyl)ethyl Chloride (13). To a stirred solution of 1-(1,5-dimethyl-2-benzimidazolyl)ethanol (4.0 g) in 50 ml of methylene chloride was added 4.4 g of phosphorus pentachloride. The exothermic reaction gently refluxed during the 1-h stirring period. The solution was then concentrated to a light yellow oil which was digested in 100 ml of methylene chloride and stirred with a slurry of aqueous sodium bicarbonate (5–10 ml) to neutralize the remaining acid. After effervescence ceased, the solution was diluted with methylene chloride (25 ml) and dried over $MgSO_4$. Rotary evaporation yielded 1.98 g (45%) of **13** as very light beige crystals: mp 107–109°; NMR ($CDCl_3$) δ 2.15 [d, 3, $CH(Cl)CH_3$], 2.55 (s, 3, 5-CH_3), 3.80 (s, 3, NCH_3), 5.40 [q, 1, $CH(Cl)CH_3$], 7.50 (m, 3, H-4, -6, -7).

Anal. Calcd for $C_{11}H_{13}ClN_2$: C, 63.31; H, 6.24; N, 13.43; Cl, 17.02. Found: C, 63.11; H, 6.17; N, 13.26; Cl, 17.24.

1-(1,5,6-Trimethyl-2-benzimidazolyl)ethyl Chloride (14). Treatment of 4,5-dimethyl-1,2-diaminobenzene with lactic acid and HCl[29] gave 1-(5,6-dimethyl-2-benzimidazolyl)ethanol in 68% yield, mp 219–221° (lit.[30] 221–222°). Following the procedures of Skolnick, Miller, and Day,[26] dimethyl sulfate and base gave 1-(1,5,6-trimethyl-2-benzimidazolyl)ethanol, mp 138–140° (93% yield), which was converted to **14** by the procedure of Skolnick, Miller, and Day,[26] mp 127–130°. The crude chloride was used directly for kinetic measurements.

1-(1-Methyl-5-pyrazolyl)ethanol. A solution of 6.6 g of 1-methylpyrazole in 450 ml of anhydrous ether was stirred under nitrogen in an ice bath as 0.1 mol (59 ml of a 1.69 M solution of *n*-butyllithium in hexane) in 50 ml of ether was added dropwise. Stirring was continued for 2 h, as formation of a bright yellow precipitate was observed. Acetaldehyde (11.9 g) was added cautiously. The ice bath was removed and the reaction mixture was stirred for an additional 15 min. Water (150 ml) was added, the layers were separated, and the aqueous layer was washed with chloroform (4 × 75 ml). The organic layers were collected and dried ($MgSO_4$), and the solvents were evaporated. The residue was distilled under vacuum to yield 3.5 g (3) of 1-(1-methyl-5-pyrazolyl)ethanol: bp 93–94° (0.5 mm); NMR (CCl_4) δ 1.48 (d, J = 6 Hz, 3, CH_3CHOH–), 3.68 (s, 3, NCH_3), 4.4 (bs, 1, –OH), 4.73 (q, J = 6 Hz, 1, CH_3CHOH–), 5.98 (d, J = 2 Hz, 1, 4-H), 7.03 (d, J = 2 Hz, 1, 3-H).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.20; H, 7.99; N, 22.20. Found: C, 57.27; H, 7.72; N, 22.34.

1-(1-Methyl-5-pyrazolyl)ethyl Chloride (15). To a solution of 0.6 g of thionyl chloride in 10 ml of 1,2-dichloroethane was carefully added 0.63 g of 1-(1-methyl-5-pyrazolyl)ethanol in ca. 1 ml of the solvent. The mixture was stirred and heated under reflux for 30 min. It was cooled and 0.5 g (0.005 mol) of triethylamine was added dropwise. The solution was cooled and the precipitated triethylamine hydrochloride was removed by filtration and then rinsed with a small amount of cold solvent. Evaporation of the solvent gave 0.70 g (98%) of crude 1-(1-methyl-5-pyrazolyl)ethyl chloride (**15**) which was used directly for kinetic studies: NMR ($CDCl_3$) (no alcohol present) δ 7.47 (d, J = 2 Hz, 1, 3-H), 6.22 (d, J = 2 Hz, 1, 4-H), 5.12 (q, J = 6.5 Hz, 1, CH_3CHCl–), 3.85 (s, 3, NCH_3), 1.87 (d, J = 6.5 Hz, 3, CH_3CHCl–).

1-(1,3-Dimethyl-5-pyrazolyl)ethanol. The procedure of Burness[31] for the preparation of 1,3-dimethylpyrazole led to a mixture of the 1,3- and 1,5-dimethyl isomers composed of roughly two-thirds of the 1,3 product by NMR. A solution of 14 g of this mixture (ca. 9.3 g or 0.097 mol of the 1,3-dimethylpyrazole) in 450 ml of anhydrous ether was stirred in an ice bath as 0.11 mol (65 ml of a 1.69 M solution) of butyllithium in 50 ml of anhydrous ether was added dropwise. Cooling and stirring were continued for 2 h after addition was complete. Three 5-ml portions of acetaldehyde were syringed into the flask, and stirring was continued for 15 min. Saturated ammonium chloride solution (150 ml) was added and the layers were separated. The aqueous layer was extracted with methylene chloride (4 × 75 ml). The organic layers were combined and dried, and the solvents were removed. Distillation afforded first a mixture of 1,5-dimethylpyrazole and unreacted 1,3-dimethylpyrazole boiling at 37–43° (1 mm). The higher boiling fraction [>90° (1 mm)] was redistilled to yield 3.55 g (26%, based on the amount of 1,3-dimethylpyrazole originally present) of 1-(1,3-dimethyl-5-pyrazolyl)ethanol: bp 125–127° (1 mm); NMR ($CDCl_3$) δ 1.45 (d, J = 6.5 Hz, 3, CH_3CHOH–), 2.08 (s, 3, C_3CH_3), 3.62 (s, 3, NCH_3), 4.70

Table III. Rate Constants for Solvolyses in 80% Ethanol

Compd solvolyzed	Temp, °C	k, s^{-1}
1	24.83	$1.28 \pm 0.02 \times 10^{-4}$
	24.83	$1.27 \pm 0.02 \times 10^{-4}$
2	24.93	$5.88 \pm 0.03 \times 10^{-3}$
3	24.93	$2.56 \pm 0.01 \times 10^{-4}$
4	75.10	$1.65 \pm 0.02 \times 10^{-3}$
	75.10	$1.69 \pm 0.02 \times 10^{-3}$
5	75.03	$1.21 \pm 0.02 \times 10^{-2}$
	75.03	$1.19 \pm 0.02 \times 10^{-2}$
6[a]	75.50	$1.10 \pm 0.01 \times 10^{-5}$
	75.50	$1.08 \pm 0.01 \times 10^{-5}$
7[a]	75.45	$4.34 \pm 0.2 \times 10^{-5}$
	75.45	$4.20 \pm 0.2 \times 10^{-5}$
8	25.00[b]	2.55×10^{-5}
	45.01	$2.38 \pm 0.01 \times 10^{-4}$
	45.02	$2.32 \pm 0.01 \times 10^{-4}$
	59.97	$1.05 \pm 0.01 \times 10^{-3}$
	75.00	$4.15 \pm 0.02 \times 10^{-3}$
9	25.30	$2.59 \pm 0.02 \times 10^{-4}$
	25.31	$2.56 \pm 0.02 \times 10^{-4}$
10	24.98	$7.19 \pm 0.03 \times 10^{-5}$
	24.99	$7.07 \pm 0.01 \times 10^{-5}$
11	25.06	$1.14 \pm 0.01 \times 10^{-4}$
	25.08	$1.13 \pm 0.01 \times 10^{-4}$
12	25.00[b]	7.45×10^{-6}
	45.0	$8.84 \pm 0.10 \times 10^{-5}$
	60.0	$3.62 \pm 0.10 \times 10^{-4}$
	75.0	$1.83 \pm 0.06 \times 10^{-3}$
13	25.00[b]	6.07×10^{-5}
	45.0	$5.57 \pm 0.06 \times 10^{-4}$
	60.0	$2.81 \pm 0.03 \times 10^{-3}$
14	25.00	$6.17 \pm 0.01 \times 10^{-4}$
15	25.04	$3.38 \pm 0.03 \times 10^{-4}$
	25.08	$3.45 \pm 0.01 \times 10^{-4}$
16	25.08	$1.269 \pm 0.002 \times 10^{-3}$
	25.08	$1.282 \pm 0.009 \times 10^{-3}$

[a] Rates measured using sealed ampules. [b] Extrapolated from data at other temperature.

(q, J = 6.5 Hz, 1, CH_3CHOH–), 5.13 (bs, 1, OH), 5.78 (s, 1, 4-H). The alcohol was characterized as the p-nitrobenzoate derivative: mp 106–107° (from hexane); NMR ($CDCl_3$) δ 1.73 (d, J = 7 Hz, 3, $CH_3CHOPNB$–), 2.23 (s, 3, C_3CH_3), 3.83 (s, 3, NCH_3), 6.12 (superimposed on q, 1, 4-H), 6.29 (q with superimposed s, J = 7 Hz, 1, $CH_3CHOPNB$–).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 57.96; H, 5.09; N, 14.64.

1-(1,3-Dimethyl-5-pyrazolyl)ethyl Chloride (16). The 1-(1,3-dimethyl-5-pyrazolyl)ethanol was converted to the chloride as above, using dichloroethane as solvent. The solvent was evaporated to yield the chloride quantitatively. The compound was utilized directly for kinetic studies: NMR (CCl_4) δ 1.82 (d, J = 7 Hz, 3, CH_3CHCl–), 2.14 (s, 3, C_3CH_3), 3.73 (s, 3, NCH_3), 4.98 (q, J = 7 Hz, 1, CH_3CHCl–), 5.87 (s, 1, 4-H).

Kinetic Methods. Kinetic methods have been described previously.[4,13,32] All rate methods were carried out at constant pH using a Radiometer automatic titrator (Model TTT 1c). The newly determined rate constants are assembled in Table III.

Registry No.—**1**, 55968-39-3; **2**, 51270-91-8; **3**, 57527-74-9; **4**, 57527-75-0; **5**, 57527-76-1; **6**, 23516-72-5; **7**, 57527-77-2; **8**, 57527-78-3; **9**, 57527-79-4; **10**, 57527-80-7; **11**, 57527-81-8; **12**, 58282-03-4; **13**, 57527-82-9; **14**, 57527-83-0; **15**, 57527-84-1; **16**, 57527-85-2; 2-methyl-3-acetylfuran, 16806-88-5; 1-(2-methyl-3-furyl)ethanol, 57527-86-3; p-nitrobenzoyl chloride, 122-04-3; 2,5-dimethyl-3-acetylfuran, 10599-70-9; 1-(2,5-dimethyl-3-furyl)ethanol, 38422-61-6; 1-(5-methyl-3-thienyl)ethanol, 57527-87-4; 4-bromo-2-methylthiophene, 29421-92-9; 1-(2-benzothiazolyl)ethanol, 17147-80-7; benzothiazole, 95-16-9; p-toluenesulfonyl chloride, 98-59-9; 6-methylbenzothiazole, 2942-15-6; 6-methylbenzothiazole-2-carboxylic acid, 3507-18-4; 1-(6-methyl-2-benzothiazolyl)ethanol, 54469-51-1; 1-(5-methyl-2-benzothiazolyl)ethanol, 57527-88-5; 5-methylbenzothiazole, 2942-16-7; 1-(4-methyl-2-benzothiazolyl)ethanol, 57527-89-6; 4-methylbenzothiazole-2-carboxylic acid, 3507-47-9; 1-(1,5-dimethyl-2-benzimidazolyl)ethanol, 57527-90-9; N-methyl-2-amino-4-methylaniline, 39513-19-4; lactic acid, 50-21-5; phosphorus pentachloride, 10026-13-8; 4,5-dimethyl-1,2-diaminobenzene, 3171-45-7; 1-(1,5,6-trimethyl-2-benzimidazolyl)ethanol, 57527-91-0; 1-(1-methyl-5-pyrazolyl)ethanol, 57527-92-1; 1-methylpyrazole, 930-36-9; 1-(1,3-dimethyl-5-pyrazolyl)ethanol, 57527-93-2; 1,3-dimethylpyrazole, 694-48-4; 1,5-dimethylpyrazole, 694-31-5; 1-(1,3-dimethyl-5-pyrazolyl)ethanol p-nitrobenzoate, 57527-94-3.

References and Notes

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Hammett and Taft Substituent Constants for the Mesylate, Tosylate, and Triflate Groups

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The Hammett σ_p values for the mesylate (1), tosylate (2), and triflate groups (3) were determined by titration of the appropriate benzoic acids and found to be +0.33, +0.29, and +0.47, respectively. Taft σ_I values were determined by ^{19}F NMR of the appropriately substituted 3-fluorophenylsulfonate esters and found to be 1, +0.61; 2, +0.54, 3, +0.84. By interpolation using pK_a data for a number of substituted acetic acids, the value of σ^* for the $CF_3SO_2OCH_2$– group was found to be +1.98. The possible nature and origin of these values are discussed and applied to the relative leaving group ability of the various sulfonate esters in SN1 reactions.

Sulfonate esters are often used in synthetic reaction schemes and mechanistic studies because of their superior leaving ability and ease of displacement by a wide variety of nucleophiles. Despite their widespread use, little is known about the electronic effects of the most important groups, namely, methanesulfonate (mesylate, 1), *p*-toluenesulfonate (tosylate, 2), and the recently developed trifluoromethanesulfonate (triflate,[1] 3), which give rise to their superior leaving ability and ease of displacement. The electronic effects of a substituent group can be conveniently divided into those of electron donation and withdrawal and are commonly expressed in terms of the Hammett σ_p and Taft σ_I and σ_R parameters.[2] Although a few σ values for some sulfonate esters have appeared in widely scattered reports,[3-5] no systematic data exist on the substituent constants of sulfonate groups. We have, therefore, determined σ_p, σ_I, and σ_R for the groups 1–3 and have also employed a number of chemical probes in order to elucidate the possible origin and nature of the electronic effects of these groups and thereby possess some basis for comparison not only of sulfonate esters among themselves but also among other sulfur containing groups such as the sulfones and thioethers.

Results and Discussion

Hammett σ_p constants were obtained by the standard technique[6] of titration of appropriately para-substituted benzoic acids in 50% (v/v) aqueous ethanol. A least-squares plot of the pK_a' vs. σ_p for a series of standard compounds is shown in Figure 1. Measurement[7] of pK_a' for the desired sulfonyloxy-substituted benzoic acids and interpolation using Figure 1 resulted in the σ_p values shown in Table I. Taft σ_I values were also obtained by standard techniques[8] using the ^{19}F NMR shift of appropriately substituted *m*-fluorobenzenes. These results are also shown in Table I. The values of σ_p obtained in this study are in good agreement with the values in the literature for 1[5] and for 3,[4] as is the value of σ_I for 2.[2,3] However, our value of σ_I = 0.84 for 3 determined by ^{19}F NMR differs substantially from the value of 0.58 given by Yagupol'skii.[4,9] Because of this discrepancy and because of some questions regarding the theoretical validity[13] of ^{19}F NMR as a tool for determining σ_I, we determined σ_I for 3 by a second independent means. This involved measurement of the pK_a's of appropriately substituted acetic acids by nonaqueous titration in 2-propanol, correlation of the pK_a's with known σ^* values,[14] and interpolation of the pK_a of $CF_3SO_2OCH_2COOH$. The results are given in Figure 2 and Table II. The Taft σ_I value can be computed from the experimentally observed σ^* value by means of the well-known relationship[2] $\sigma_{I(x)} = 0.450\ \sigma^*_{(xCH_2)}$ to be $\sigma_{I(3)}$ = 0.89, which is in substantial agreement with the value found by ^{19}F NMR in Table I.

The substituent constants and the nature of sulfonate esters can best be discussed by division of their properties into those of electron-withdrawing and donating ability and comparison with sulfone and alkoxy substituents. The relevant data are assembled and summarized in Table III. As seen by examination of the data in Table III, the positive sign of the Hammett σ_p constants for the mesylate, tosylate, and triflate groups indicates that the sulfonate esters are deactivating toward electrophilic aromatic substitution, but ortho–para directing because of the negative sign of σ_R. Indeed, this observation is in accord with experimental evidence that phenyl tosylate is nitrated simply with concentrated nitric acid,[15] whereas phenyl mesylate requires treatment with a mixture of KNO_3 and H_2SO_4 for 24 h;[16] by varying the ratio of KNO_3/H_2SO_4, either a 4-nitro or a 2,4-dinitrophenyl mesylate could be obtained.

Table I. Hammett σ_p and Taft σ_I Values for the Mesylate, Tosylate, and Triflate Groups

Substituent	pK_a of p-XC_6H_4COOH[c]	σ_p	$\delta_{m\text{-}XC_6H_4F}$,[a,d] ppm	σ_I
CH_3SO_2O– (1)	5.18	+0.328	181.3	+0.61
$CH_3C_6H_4SO_2O$– (2)	5.25	+0.280	155.5	+0.54
CF_3SO_2O– (3)	4.97	+0.473	259.0	+0.84[e] +0.89[b]

[a] In 5% CCl_4 at 25° downfield from internal C_6H_5F. [b] Calculated from σ^*; see text. [c] Registry no. are, respectively, 28547-25-3, 51804-15-0, 32578-34-0 [d] Registry no. are, respectively, 57606-63-0, 57606-64-1, 57606-65-2. [e] This value of σ_I is further confirmed by a least-squares plot of $\pi_{H(CH_2X)}$ vs. $\sigma_{I(X)}$.[14]

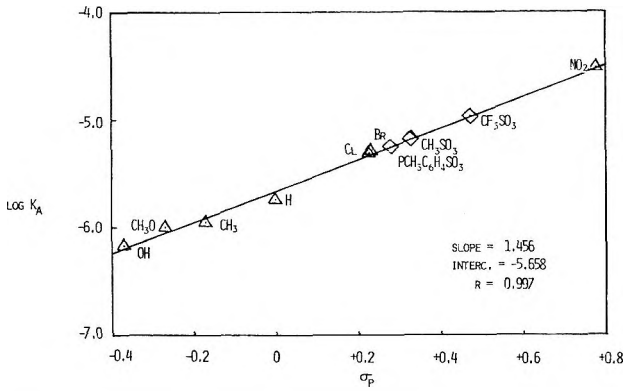


Figure 1. Log K_a vs. σ_p for p-XC_6H_4COOH.

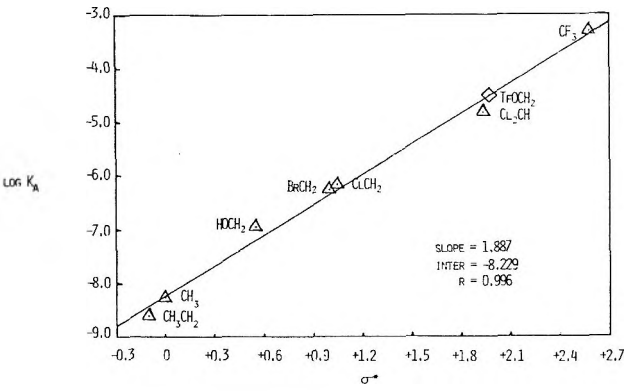
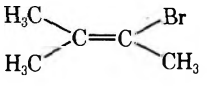


Figure 2. Log K_a vs. σ^* for XCOOH.

Phenyl triflate, possessing the most positive σ_p of the three esters, nitrates first at the 4 position and next at the 2 position, but only under forcing conditions. The strong inductive electron-attracting ability of the triflate group is also shown by the relative rate of bromination of 2-bromo-3-methyl-2-butene (**4**) and 3-methyl-2-buten-2-yl triflate (**5**), with **4** brominating three times as fast as **5** in CCl_4 at 25 °C.[17]



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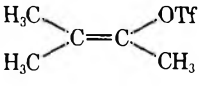

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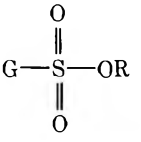
The inductive effect, arising out of differences in electronegativity of the elements, involves the σ framework of the molecule and is measured by the Taft parameter σ_I. The resonance effect operates through the π orbitals of the molecule and is a crude measure of the p_π–p_π interactions occurring within the molecule. The σ_R values for the triflate, mesylate, and tosylate groups indicate that all three groups are capable of donating electrons. What is somewhat surprising is the magnitude of the effect in the case of triflate, when contrasted to the behavior of other groups attached to a phenyl ring via an oxygen atom. It is well known that the σ_R value for the methoxy group is negative; the methoxy group interacts with the phenyl ring via $2p_\pi$–$2p_\pi$ interactions, donating electrons from the p atomic orbitals of oxygen. It is also known from photoelectron spectroscopy[20] that the two highest occupied molecular orbitals of the phenyl ring in anisole become split in energy, indicating strong interaction of the oxygen with the phenyl ring. In the case of the OCF_3 group, photoelectron spectroscopy reveals that the two highest occupied molecular orbitals are degenerate. The σ_R value (see Table III) for the CF_3 group indicates that the CF_3 group is strongly electron withdrawing by resonance. Even when present as the ether, OCF_3, its effect is dominant.[21] Sheppard has found the O=S(=O)CF_3 group to be one of the most electron-withdrawing neutral groups (σ_p = 0.93) known.[18] Thus, when substituted for the CF_3 group in a phenyl "ether", its effect should be at least as great as the CF_3 group, and no p_π–p_π interaction of the oxygen p atomic orbitals with the benzene ring should be expected. However, as shown by experiment, exactly the opposite is observed. One must then either assume that the O=S(=O)CF_3 group has no effect on the oxygen atom and that the electron donation from the triflate group is occurring solely from the p atomic orbitals of the oxygen atom or, more likely, that extensive delocalization of electrons is occurring through the sulfur atom of the triflate group out to the "sulfone" oxygen atoms. The sulfur atom of a sulfonate has no electrons to donate by resonance, since all of its electrons are used in forming the approximately tetrahedral σ framework of the sulfonate group and in double bonds to the two "sulfone" oxygen atoms. If the sulfur atom could itself donate electrons, then sulfone groups would be expected to have a negative σ_R, which they do not have (see Table III).

Table II. pK_a of Substituted Acetic Acids in *i*-PrOH at 25 °C

Registry no.	Compd	pK_a	σ^*[a]
79-09-4	CH_3CH_2COOH	8.61	−0.100
64-19-7	CH_3COOH	8.27	0.000
79-14-1	$HOCH_2COOH$	6.94	0.555
79-08-3	$BrCH_2COOH$	6.25	1.000
79-11-8	$ClCH_2COOH$	6.16	1.050
79-43-6	$Cl_2CHCOOH$	4.81	1.940
57606-66-3	$CF_3SO_2OCH_2COOH$	4.50	1.947[b]
76-05-1	CF_3COOH	3.31	2.58

[a] From ref 14. [b] This work.

Recently, Crossland[22] has presented evidence that the leaving ability of various sulfonate esters under limiting SN1 solvolysis conditions is correlated with the inductive effect of the group, G, on sulfur. However, Crossland used



σ_m to estimate the inductive effect of the group, G. If only inductive effects were operating, then σ_I would be a far better estimate of electron-withdrawing ability than σ_m, which contains about 22% resonance contribution.[23] However, inspection of the σ_I data for the group, G, on sulfur would lead one to predict that, contrary to fact, fluorosulfonates solvolyze faster than triflates.

Perhaps a better explanation of leaving ability and electronic influence of the sulfonate esters can be had by examining the effect of the group, G, on the d orbitals of sulfur, through which sulfur can interact with oxygen by virtue of $3d_\pi$–$2p_\pi$ bonding.[24] It is well known that attachment of electronegative ligands to sulfur contracts the d orbitals of sulfur.[24] In a sulfonate ester the sulfur is bonded to three oxygen atoms; the effect of the fourth group, G, as an electronegative ligand would be to further contract the d orbitals of sulfur, allowing still better overlap of the "sulfone" and "ester" oxygen 2p atomic orbitals with the sulfur 3d orbitals, and thus further enhancing the $3d_\pi$–$2p_\pi$ interactions. Indeed, the σ_R for the tosylate and mesylate groups are approximately equal, but the σ_R for the triflate group is much larger. This increase in resonance is probably due to the greater effect of the CF_3 group as an electronegative ligand on the $3d_\pi$–$2p_\pi$ interactions of the "sulfone" and "ester" oxygen atoms. In effect, a greater delocalization of

Table III. Summary of Substituent Constants for Various Sulfur and Oxygen Containing Substituents

Substituent (x)	$\sigma_{p(=)}$	$\sigma_{R(x)}$	$\sigma_{I(x)}$	$\sigma_{m(x)}$	$C^*_{(xCH_2)}$	Ref
CH_3SO-	+0.33	−0.28	+0.61			This work
	+0.36			+0.39		5
C_6H_5SO-	+0.33			+0.36		5
p-$CH_3C_6H_4SO-$	+0.29	−0.21	+0.54			This work
			+0.59		+1.31	3
CF_3SO-	+0.47	−0.36	+0.84 (0.89)		+1.98	This work
	+0.53	−0.05	+0.58	+0.56		4
CH_3S-	+0.72	+0.14	+0.62	+0.65		2, 18
p-$CH_3C_6H_4S-$	+0.67	+0.12	+0.55			19
CF_3S-	+0.93	+0.22	+0.69			18
CH_3O-	−0.27	−0.47	+0.21	+0.12		2,18
CF_3O-	+0.35	−0.13	+0.51	+0.40		18
CH_3-	−0.17	−0.10	+0.06	−0.07	0.00	2
CF_3-	+0.54	+0.12	+0.39			2, 18

electrons from the R groups via the single S–OR bond through sulfur to the "sulfone" oxygens occurs in the triflate group than in the mesylate or tosylate groups.

Using a methyl sulfonate as a model, a qualitative mechanism can be inferred for the limiting SN1 solvolysis of sulfonate esters. As the O–R bond lengthens, the "ester" oxygen begins to rehybridize from sp^3 to sp^2. As the lone pair electrons on the "ester" oxygen begin to develop more p character, aided by delocalization into the lowest lying empty d orbital of sulfur, the π framework begins to contract owing to its increase in s character. Eventually, the O–R bond is broken and the charge spread equally over the three oxygen atoms of the sulfonate anion. Internal return and scrambling of the ester oxygen can then occur depending on the nucleophilicity of the sulfonate anion and the stability of the carbonium ion generated.

Using such a mechanism, it can readily be seen why a fluorosulfonate ester solvolyzes slower under limiting SN1 conditions than a triflate ester. During the initial stage of the reaction, the developing p lobe of the "ester" oxygen must compete with back-bonding from the fluorine atom of the fluorosulfonate for the lower lying empty d orbitals of sulfur. The σ_I of a fluorine atom is +0.52 whereas that of a CF_3 group is +0.41. Thus, although the electron-withdrawing ability of a fluorine atom is much greater than that of a CF_3 group, and presumably the d orbitals of sulfur in a fluorosulfonate ester are more contracted with fluorine present, a fluorosulfonate solvolyzes slightly slower owing to $3d_\pi$–$2p_\pi$ backbonding from fluorine to sulfur.[25]

The carbon atoms of mesylate and tosylate would be expected to have less of an effect on the sulfur d orbitals and thus would be expected to have a smaller negative σ_R and solvolyze slower, as found by experiment. Since the σ_R constants for the tosylate and mesylate groups are nearly identical, this implies that the tolyl and methyl groups affect $3d_\pi$–$2p_\pi$ interactions approximately to the same extent, and leaving ability then becomes dependent on the difference in σ_I of these two substituents.

As an extension of these ideas, a tentative explanation for the electron-withdrawing effect of the CH_3SO_2 or CF_3SO_2 groups can be offered. In these groups fewer electronegative ligands are present than in the sulfonate esters. The effect on $3d_\pi$–$2p_\pi$ bonding may be to raise the energy of the lowest unoccupied d orbital on sulfur to such a level that resonance through sulfur to the sulfone oxygens is inhibited, thus making the sulfur atom which is still in a promoted hexavalent state into an electron sink via its empty d orbitals. With even fewer ligands on sulfur, as in the case of substituted sulfides, spare pairs of electrons become available for donation via $3p_\pi$–$2p_\pi$ interactions and the sign of σ_R becomes negative for most groups incapable of strong interactions with sulfur, i.e., $\sigma_{R(S-CH_3)} = -0.28$ vs. $\sigma_{R(S-CF_3)} = +0.17$, although the net flow of electrons using an spd basis set is still in the direction of sulfur,[26] i.e., $\sigma_{p(S-CH_3)} = 0.00$.[2]

Experimental Section

General. All boiling points are uncorrected. ^1H NMR spectra were recorded on a Varian Associates A-60 spectrometer and data are given in δ (parts per million) relative to internal tetramethylsilane (δ 0) as indicated. ^{19}F NMR spectra were recorded on a Varian Associates A-56/60A spectrometer operating at 56.40 Hz at 25 ± 1 °C relative to internal fluorobenzene (C_6H_5F, δ 0). All ir spectra were recorded on a Beckman IR-5A and are reported in wavenumbers (cm^{-1}) calibrated to the 1603-cm^{-1} line of polystyrene. Either a Varian Aerograph 90-P or 920 gas chromatograph using a 5 ft × 0.25 in. 10% SF-96 on 60/80 Chromosorb W was used for preparative work. A 6 ft × 0.125 in. 10% UC-W98 column was used for flame ionization GLC analysis performed on a Hewlett-Packard 700 laboratory chromatograph coupled to a Hewlett-Packard 3370B integrator. Titration curves were recorded on a Metrohm Herisau E 436 potentiograph using an E 436 D automatic pipet and EA 120X combination glass electrode.

Reagents. p-Nitrobenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, p-methoxybenzoic acid, p-methylbenzoic acid, dichloroacetic acid, and bromoacetic acid were purchased from Matheson Coleman and Bell. p-Bromobenzoic acid and propanoic acid were purchased from Eastman. p-Toluenesulfonic acid was purchased from both Eastman and Matheson Coleman and Bell and was used without further purification. m-Fluorophenol was purchased from Sigma Chemical Co. and was distilled before use. Acetic acid was purchased from Allied Chemical Co. Trifluoroacetic acid, glycolic acid, glycine, and methanesulfonyl chloride were purchased from Aldrich Chemical Co. p-Toluenesulfonyl chloride was purchased from Matheson Coleman and Bell and was purified according to Pelletier.[27] Bromine, sodium nitrite, chloroacetic acid, sodium hydroxide, and potassium hydroxide were purchased from Mallinckrodt.

Purification of Benzoic Acids Used. With the exception of anisic acid, the benzoic acids were recrystallized first from ethanol and then from water, pretreating each solution with charcoal, then

sublimed at 0.01 mm. Anisic acid was purified by dissolution in water made alkaline with excess NaOH, the solution warmed to 40 °C, and $KMnO_4$ crystals added with stirring until the purple color of MnO_4^- persisted for 5 min. The solution was then cooled to 25 °C and $NaHSO_3$ crystals added until the purple color was discharged. The MnO_2 produced was filtered and the anisic acid precipitated from the colorless filtrate by addition of excess concentrated HCl. The anisic acid was then recrystallized from water to yield 3.8-cm needles which were collected by suction filtration, air dried, and sublimed in vacuo at 0.01 mm.[28] All of the benzoic acids used had melting points in good agreement with accepted literature values.

Acetic, propanoic, chloroacetic, bromoacetic, dichloroacetic, and trifluoroacetic acids were fractionally distilled either at ambient pressure or at reduced pressure through a 10-cm Vigreux column taking only a center cut whose boiling point corresponded to accepted literature values. Glycolic acid and glycine were of reagent quality and were used without further purification.

Determination of pK_a'.[29] Distilled water was treated with $KMnO_4$, refluxed for 1 h, and then twice distilled using an Ascarite tube for protection from atmospheric CO_2. Ethanol was dried according to Manske[30] and protected during distillation from atmospheric moisture and CO_2 by tubes filled with Drierite and Ascarite. The water and ethanol were thermostated to 20 °C in 1-l. volumetric flasks prior to mixing to make 50% aqueous ethanol (v/v). Approximately 0.07 g of the substituted benzoic acids were dissolved in 100 ml of the solvent and then 30-ml aliquots were titrated at 25 ± 1 °C with carbonate-free NaOH prepared in the same solvent. The midpoint of the titration curve was read graphically to determine the pK_a'. In no titration run did the resultant pK_a' differ by more than 0.01 pH unit from the average and in most runs no detectable difference was observed. Prior to each determination the glass electrode used was standardized against two known buffers, rinsed well with distilled water, gently dried with a tissue, immersed in a blank of 50% aqueous ethanol (v/v), and finally immersed in the sample to be titrated. After each titration the electrode was again checked against two known buffers. No drift was observed in the electrode.[31]

Determination of σ^* of the Trifluoromethanesulfonyloxy Group. Owing to observed leveling of dichloroacetic acid and trifluoroacetic acid in 50% aqueous ethanol (v/v) and 80% aqueous ethanol (v/v), anhydrous 2-propanol was chosen as the titration solvent. Reagent grade anhydrous isopropyl alcohol was fractionally distilled before use while protected from atmospheric CO_2 and H_2O by an Ascarite tube and Drierite tube. Potassium hydroxide from a freshly opened bottle was dissolved in anhydrous 2-propanol and was used to titrate 0.003 M samples of substituted acetic acids dissolved in 2-propanol in a manner similar to that described for the *p*-substituted benzoic acids. The $pK_{a(i\text{-}PrOH)}$ was determined graphically from the midpoint of the titration curve.

Determination of Relative Bromination Rate. 2-Bromo-3-methyl-2-butene was prepared[32] and purified by GLC. 3-Methyl-2-buten-2-yl trifluoromethanesulfonate was prepared[33] and purified by GLC. Approximately equal volumes of 2-bromo-3-methyl-2-butene and 3-methyl-2-buten-2-yl trifluoromethanesulfonate were injected into a serum-capped vial at 25 °C containing 4 ml of CCl_4. Then five samples were withdrawn and analyzed on a flame ionization GLC to determine the relative ratio of the two components. A small amount of Br_2 in CCl_4 was injected into the vial and after complete discharge of the color of Br_2 (~10 min) five samples were withdrawn with a syringe and analyzed as before, resulting in an average value of $k_{Br}/k_{OTf} = 2.9$. Since the bromination products were not stable to the GLC conditions, the disappearance of the starting materials was used for the rate measurement.

Synthesis of Compounds. The phenylsulfonic esters were synthesized either by the pyridine method, A, or by a Schotten-Baumann reaction, B.

3-Fluorophenyl *p*-Toluenesulfonate. Method A. To 1.00 g of freshly distilled 3-fluorophenol was added an equal volume of pyridine, followed by 1.71 g of freshly purified *p*-toluenesulfonyl chloride. The mixture became warm and was heated on the steam bath for 10 min, cooled, and poured into 10 ml of H_2O. The ester precipitated at once and was filtered, dissolved in ethanol, and treated with charcoal, the charcoal was removed by filtration, and the filtrate was evaporated to dryness on the steam bath. The white solid was recrystallized from EtOH–H_2O to give 1.52 g (57%) of colorless needles: mp 47.5–48.5°; ir (Nujol mull) 1370, 1191, 1177 (S=O), 1242 (aromatic C–F); ^{19}F NMR δ 155.5; ^1H NMR (Me_2SO-d_6) δ 2.43 (s, 3), 7.60 (d of q, 8), 13.1 (br s, 1); mass spectrum *m/e* (rel intensity) 266 ($M\cdot^+$, 30), 202 (22), 156 (49), 155 (52), 91 (100).

Phenyl Trifluoromethanesulfonate. Method B. To 6.00 g of phenol in 60 ml of H_2O was added 6.00 g of NaOH and the mixture was shaken until dissolved. Then 20.22 g of trifluoromethanesulfonic anhydride dissolved in 20 ml of CCl_4 was added while stirring and cooling in an ice bath. The mixture was stirred for an additional 1.5 h, the CCl_4 layer separated in a separatory funnel, and the aqueous layer washed with 5 ml of CCl_4. The CCl_4 solution was dried over $MgSO_4$, the $MgSO_4$ filtered off, and the CCl_4 removed on a rotary evaporator at aspirator pressure: crude yield 11.72 g (81%), redistilled 9.10 g (63%); bp 87–88 °C (13 mm) [lit.[34] bp 99–100 °C (60 mm) and 51–53 °C (1 mm)[35]]; ir (neat) 1421, 1212 (S=O), 1248 (C–F), 1600, 1585, 1484, 1456 cm^{-1} (aromatic C=C).

3-Fluorophenyl Methanesulfonate. Method A. The product was recrystallized four times from EtOH–H_2O at −70 °C to obtain 0.41 g (21%) of colorless needles: mp 23.5–24.5°; ir (Nujol mull) 1379, 1182 (S=O), 1248 cm^{-1} (C–F); ^{19}F NMR δ 181.3; ^1H NMR (Me_2SO-d_6) δ 3.47 (s, 3), 7.83 (q, 4), 12.7 (br s, 1); mass spectrum *m/e* (rel intensity) 190 ($M\cdot^+$, 56), 126 (10), 112 (100), 96 (22).

3-Fluorophenyl Trifluoromethanesulfonate. Method B. The product was purified by distillation to obtain a colorless oil: bp 46–47 °C (3.6 mm) [lit.[4] 60 °C (20 mm)]; mp 11.5–12.4 °C; ir (neat) 1429, 1214 cm^{-1} (S=O); ^{19}F NMR δ 259; ^1H NMR (Me_2SO-d_6) δ 7.90 (q, 4), 12.87 (br s, 1); mass spectrum *m/e* (rel intensity) 244 ($M\cdot^+$, 62), 180 (50), 152 (11), 111 (100).

4-Carboxyphenyl *p*-Toluenesulfonate. Method B. The product was recrystallized from EtOH–H_2O as needles, 11.5 g (54%), sublimed at 149 °C (0.5 mm): mp 168–168.5 °C uncorrected (lit.[36] 167–169 °C uncorrected); ir (Nujol mull) 1686 (C=O), 1429, 1201, 1174 cm^{-1} (S=O).

4-Carboxyphenyl Methanesulfonate. Method B. The product was recrystallized from EtOH–H_2O, sublimed at 185 °C (0.2 mm): mp 219–220 °C (lit.[16] mp 224 °C corrected); ir (Nujol mull) 1684 (C=O), 1425, 1199, 1168 cm^{-1} (S=O).

4-Carboxyphenyl Trifluoromethanesulfonate. Method B. The product was recrystallized from EtOH–H_2O, 6.12 g (31.2%), sublimed at 140 °C (0.2 mm): mp 168–170 °C uncorrected (lit.[4] 175–177 °C corrected); ir (Nujol mull) 1686 (C=O), 1418, 1212 (S=O), 1250 cm^{-1} (CF_3).

4-Nitrophenyl Trifluoromethanesulfonate. Phenyl trifluoromethanesulfonate (1.00 ml) was added to a mixture of 6 ml of concentrated H_2SO_4 and 6 ml of concentrated HNO_3, precooled to 0–5 °C in an ice bath. The mixture was left at 0–5 °C for 14 h and ice then added to precipitate a white solid. This was recrystallized from EtOH–H_2O to give white plates, mp 54–55 °C (lit.[4] mp 51–52 °C, lit.[35] mp 53–54 °C).

2,4-Dinitrophenyl Trifluoromethanesulfonate. Phenyl trifluoromethanesulfonate (0.5 ml) was added to 6 ml of concentrated H_2SO_4 in a 25-ml Erlenmeyer flask and stirred. Very little ester appeared to dissolve in the H_2SO_4. Then 3 ml of concentrated HNO_3 was added at room temperature and the reaction mixture was heated for 2 h on the steam bath and quenched with ice, and the product was worked up in the same manner as 4-nitrophenyl trifluoromethanesulfonate to give plates, mp 52–53 °C (lit.[4] mp 51–52 °C). The plates were treated with 1 g of NaOH dissolved in 10 ml of EtOH and 10 ml of H_2O, heated for 30 min on the steam bath, made acidic with concentrated HCl, and concentrated on a rotary evaporator to 10 ml, and the faint yellow crystals were isolated and recrystallized from EtOH–H_2O (1:5 v/v) to give crystals, mp 114–115 °C. A mixture melting point with authentic 2,4-dinitrophenol was undepressed. An ir taken was identical with that of authentic 2,4-dinitrophenol.

Glycolic Acid Trifluoromethanesulfonate. Glycine benzyl ester *p*-toluenesulfonate[37] was diazotized[38] and treated with trifluoromethanesulfonic acid,[39] the benzyl ester removed by catalytic hydrogenolysis,[40] and the product recrystallized from CCl_4 to give white needles: mp 58–59 °C; ir (melt) 3000, 1750 (C=O), 1413, 1214, 1142 (S=O), 1242 (CF_3), 1032, 861, 814, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.98 (s, 2), 10.52 (s, 1).

Determination of Taft σ_I and σ_R substituent Parameters. The literature[8] procedure using C_6H_5F as an internal standard in CCl_4 solution was followed; σ_I was determined from the average of six runs by the equation $\delta_m^F = 0.61\sigma_I - 0.05$. The Taft σ_R parameter was determined from the equation $\sigma_p = \sigma_I + \sigma_R$.

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Registry No.—3-Fluorophenol, 372-20-3; *p*-toluenesulfonylchloride, 98-59-9; phenyl trifluoromethanesulfonate, 17763-67-6; phenol, 108-95-2; trifluoromethanesulfonic anhydride, 358-23-6; glycine benzyl ester *p*-toluenesulfonate, 1738-76-7.

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Secondary Deuterium Isotope Effects in the Solvolysis of *cis*- and *trans*-2-Acetoxycyclohexyl 2,2,2-Trifluoroethanesulfonates

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The 2,2,2-trifluoroethanesulfonates (tresylates) of specifically deuterated *cis*-2-acetoxycyclohexanol (*cis*-1βd, *cis*-1αd, *cis*-1$\beta' d_2$) and *trans*-2-acetoxycyclohexanol (*trans*-1βd, *trans*-1αd, *trans*-1$\beta' d_2$) were solvolyzed in 97 wt % trifluoroethanol at 95 and 55°C, respectively, and the secondary deuterium isotope effects were measured. The solvolysis products from the trifluoroethanolysis of the unlabeled isomeric tresylates *cis*-1 and *trans*-1 were also determined. The α effect in *trans*-1αd is similar in magnitude to the effects observed in SN2 reactions (k_H/k_D = 1.03). The β effects in *trans*-1βd and *trans*-1$\beta' d_2$ are also small (k_H/k_D = 0.98 and 1.04, respectively), reflecting the absence of significant hyperconjugative stabilization. These results are in agreement with a transition state structure closer to the oxonium ion intermediate than to the reactants. The results obtained in the solvolysis of the corresponding cis derivatives are significantly different. The α effect is large (k_H/k_D = 1.20) indicating that ionization to the solvent-separated ion pair is rate determining, while the β effects are "normal" but larger for *cis*-1βd (1.34) than for *cis*-1$\beta' d_2$ (1.23). On the basis of these results it was concluded that the cis derivative solvolyzes via a twist-boat transition state. The present work demonstrates the sensitivity of secondary deuterium isotope effects to structural changes of solvolytic transition states.

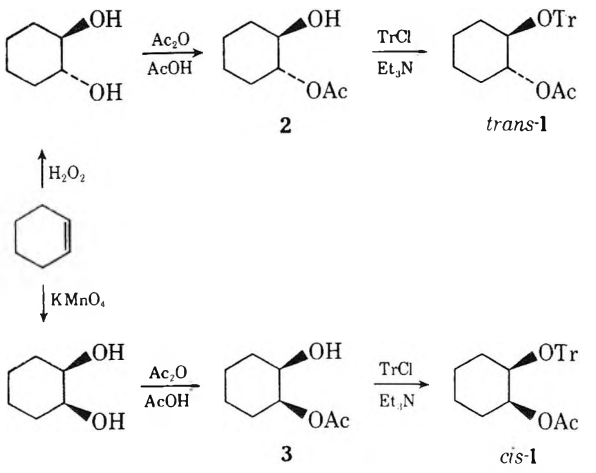
"The deuterium isotope effect has become one of the most important of the tools which physical organic chemists employ in the elucidation of the mechanisms of chemical reactions", but "a dilemma has plagued the interpretation of the experimental data" In 1961 when Westheimer wrote these lines,[1] the dilemma was associated with a spectrum of values of the ratio k_H/k_D. Regretfully, a lack of understanding of the meaning of differences in the magnitudes of observed isotope effects still pertains today.[2] In spite of a satisfactory theoretical treatment of isotope effects, primary[3] as well as secondary,[3,4] the interpretation of isotopic rate data rests mostly on the empirical comparison of these effects in systematically varied and closely related systems. The success of such an approach has been amply demonstrated by Shiner and co-workers[5] in their studies of nucleophilic substitution reactions.

We have shown[6] that the magnitude of secondary isotope effects changes in a predictable manner with the degree of bond breaking and bond making in the transition states of reactions proceeding with neighboring group participation. These studies involved mostly π and σ participation, whereas only a few data are known for n-participating systems.[7] In the present paper, we report kinetic and product studies on the trifluoroethanolysis of specifically deuterated *cis*- and *trans*-2-acetoxycyclohexyl 2,2,2-trifluoroethanesulfonates (tresylates). The solvolysis mechanism of the corresponding tosylates was elucidated in detail by Winstein,[8] which makes this substrate particularly appropriate for systematic studies of the mechanistic meaning of small differences in the k_H/k_D values.

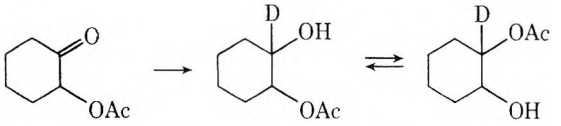
Results

Undeuterated *cis*- and *trans*-2-acetoxycyclohexyl tresylates (*trans*-**1**, *cis*-**1**) were prepared according to Scheme I using a slightly modified version of the published procedures.[9,10]

Scheme I



The synthesis of specifically deuterated substrates (*cis*-1βd, *trans*-1βd, *cis*-1αd, *trans*-1αd, *cis*-1$\beta' d_2$, *trans*-1$\beta' d_2$) could not be accomplished by the more convenient tresylation of deuterated 2-acetoxycyclohexanol, because preliminary examinations have shown that any method involving the preparation of sulfonate esters from 2-acetoxycyclohexanols leads to migration of the acetyl group.[11] In our case such a migration results in distribution of deuterium between positions 1 and 2 in the cyclohexane ring:



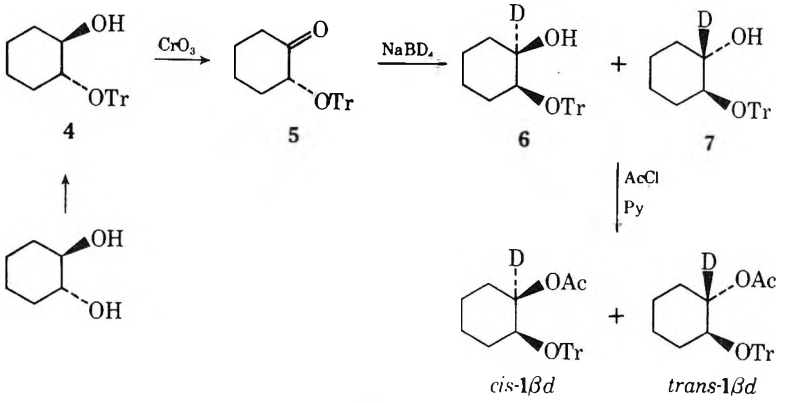
Therefore indirect synthetic routes, shown in Schemes II–IV, were developed for the preparation of specifically deuterated 2-acetoxycyclohexyl tresylates.

The synthetic scheme required the introduction of the tresyl group at an early stage of the synthesis. Fortunately no significant loss of material due to hydrolysis was observed during subsequent steps. However, some unavoidable loss of deuterium was observed during the conversion of **8** to **10**.

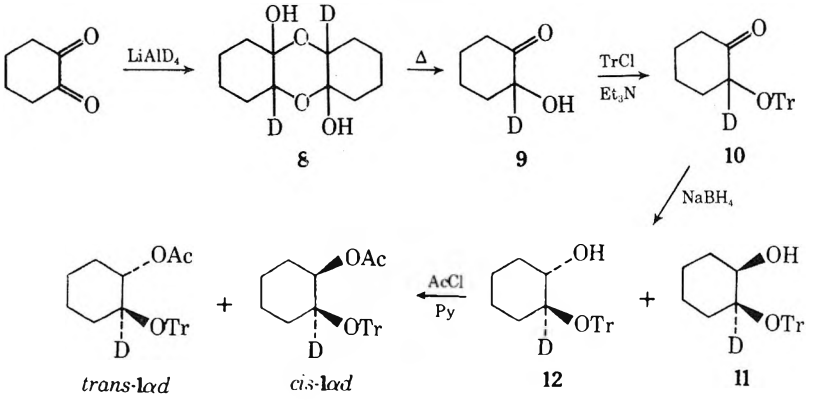
Solvolyses of *trans*-2-acetoxycyclohexyl tresylates (*trans*-**1**, *trans*-1βd, *trans*-1αd, *trans*-1$\beta' d_2$) were accomplished in 97 wt % 2,2,2-trifluoroethanol at 55 °C for 3 h (about 3 half-lives). The rates were measured potentiometrically at a constant pH.[12] Standard ampule technique in the presence of 2,6-lutidine had to be used for the less reactive tresylates *cis*-**1**, *cis*-1βd, *cis*-1αd, and *cis*-1$\beta' d_2$ (see Experimental Section for details). Clear first-order kinetic behavior was observed in all cases. The kinetic results are presented in Table I.

Table II gives the composition of solvolysis products as

Scheme II



Scheme III



Scheme IV

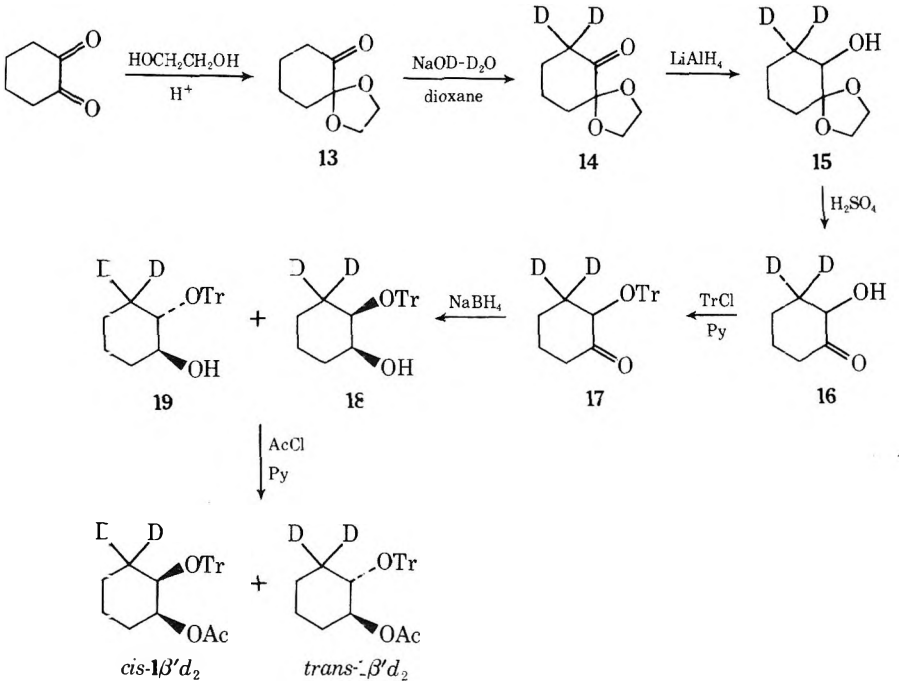
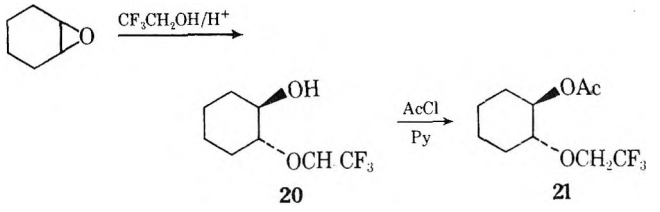


Table I. Deuterium Isotope Effects in the Solvoylsis of Some 2-Acetoxycyclohexyl Tresylates in 97% TFE

Compd	Temp, °C	$k \times 10^5$, s^{-1}	k_H/k_D[a]
cis-1βd	93	1.81 (1)[b]	1.34 (3)[b]
trans-1βd	55	21.0 (1)	0.98 (1)
cis-1αd	93	2.01 (5)	1.20 (3)
	25[c]		1.25[c]
trans-1αd	55	20.00 (8)	1.08 (1)
	25[c]		1.063[c]
cis-1β'd_2	93	1.98 (5)	1.28 (6)
trans-1β'd_2	55	19.75 (8)	1.04 (1)

[a] The values are corrected to 100% deuterium content. Rate constants for undeuterated compounds *trans*-1 and *cis*-1 were 2.050 ± 0.006 × 10^{-4} s^{-1} at 55°C and 2.43 ± 0.04 × 10^{-5} s^{-1} at 93 °C, respectively. [b] The errors are given as standard errors, e.g., 1.34 (3) = 1.34 ± 0.03. The values of the isotope effects were calculated using three (for *cis*-1βd, *cis*-1αd, *cis*-1β'd_2) to six (for *trans*-1βd, *trans*-1αd, *trans*-1β'd_2) individual rate constants for both deuterated and undeuterated compounds. [c] Calculated from the observed values at higher temperatures assuming no isotope effect in the Arrhenius preexponential factor. For the relative temperature independence of β-deuterium effects see ref 5, p 148.

established by gas chromatography. For comparison the necessary trifluoroethyl ethers (**20, 21**) were synthesized as shown below:



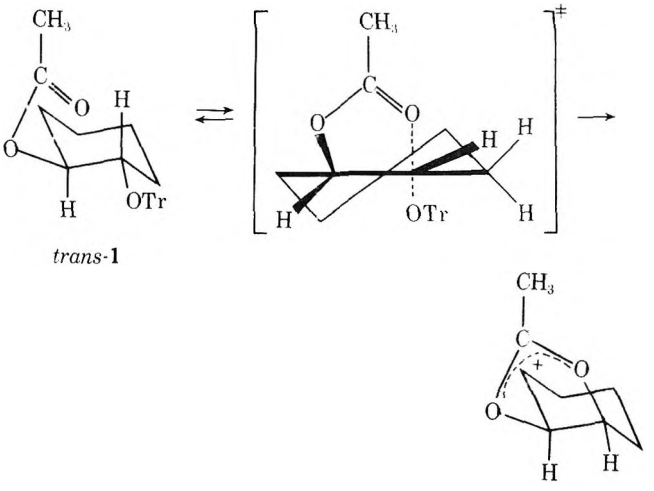
Discussion

The results obtained in the course of this work leave little doubt that in the solvolysis of *cis*- and *trans*-2-cyclohexyl tresylate small differences in the values of secondary deuterium isotope effects can be correlated with different transition state structures.

Only the trans isomer of the two isomeric acetoxy tresylates solvolyzes by acetoxy participation and the formation of a bridged intermediate.[8,13]

Table II. Solvolysis Products of *cis*- and *trans*-2-Acetoxycyclohexyl Tresylates in 97 wt % TFE

Substrate	Products			
trans-1	100%			
cis-1	55.6%	28.4%	4.4%	5.1% 6.5%



In concert with this mechanism the magnitude of the observed α effect is characteristic for direct displacement reactions involving partial bond formation with the entering internal nucleophile. Such small effects have been observed

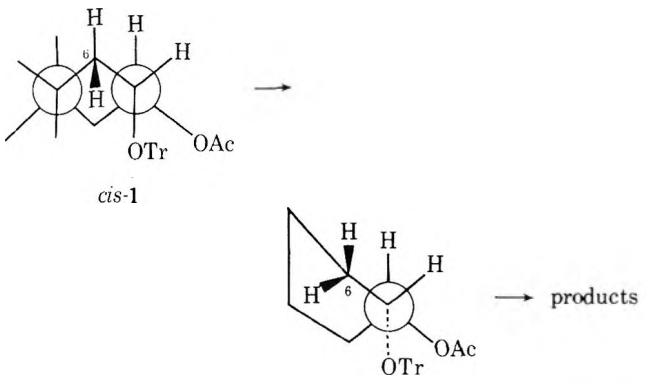
previously in SN2 reactions[14] and in n-participating solvolyses.[6] The rate effects of deuterium substitution in the β positions also support the established mechanistic pathway. The structure of the bridged cation, and consequently of the transition state leading to it, implies charge delocalization. In a delocalized bridged ion stereoelectronic factors render additional hyperconjugative stabilization by adjacent C–H(D) bonds superfluous.[12a,15] The β-isotope effects reflect this situation in detail. Labeling at C_2 affords a small rate increase indicative of greater inductive electron withdrawal from the C–D bond relative to the C–H bond.[16] The steric orientation of this bond also minimizes hyperconjugation. The rate effect of replacing deuterium for protium at C_6 is also small but positive (k_H/k_D = 1.04) revealing some hyperconjugative interaction with C_1. This is not surprising since bridging is probably not complete in the transition state and steric orientation of the C_6–D bonds does not preclude hyperconjugation. The observed effect parallels those in other delocalized transition states.[17] It is likely that here, as in *cis*-4-*tert*-butylcyclohexyl tosylate solvolysis,[5] only the axial C_6–D bond is properly oriented for interaction with the reaction center.

From the product composition it can be inferred that 97% TFE behaves similar to wet acetic acid. For this solvent Winstein proposed[9] the intermediacy of orthoacetate which is formed from the initial acetoxonium ion by attack of water and loss of proton. This reaction affords *cis*-2-acetoxycyclohexanol, which was in our case the only product formed.

Inspecting the results obtained with the cis isomer an entirely different picture emerges. Here acetoxy participation is absent and the solvolysis is ~10^3 times slower (at 50 °C). The α effect is close to its maximum value for the solvolysis of sulfonate esters (~1.23) which is characteristic for rate-determining formation of the solvent separated ion pair.[18]

The stereochemistry of the substitution products (90% inversion and 10% retention) also supports the formation of the solvent separated ion-pair intermediate. The substitution pathway should in this case be similar to the one observed in reactions of simple cyclohexyl derivatives in solvents of high ionizing power and low nucleophilicity.[19]

Both β effects are normal in magnitude and direction. However the C_6-d_2 compound *cis*-1$\beta'd_2$ shows a smaller effect than the C_2-d_1-tresylate *cis*-1βd (1.23 vs. 1.34). This, we believe, can be rationalized as follows. In a chair conformation the axial and equatorial deuteriums at C_6 are not equivalent for hyperconjugation[20] and the effects should be 0.944 (equatorial) and 1.174 (axial), respectively.[21] The maximal effect in this configuration should be 0.94 × 1.174 = 1.11, which is considerably less than observed. However, *cis*-2-acetoxycyclohexyl tresylate, with two bulky groups cis to each other, should prefer a twist-boat conformation. In this conformation the dihedral angles between the C_6–D bonds and the developing p orbital at C_1 are not optimal for hyperconjugation but both deuteriums can interact partially, leading to an effect of intermediate value.[22]



The larger effect with the d_1 compound can be ascribed to rate-determining elimination in combination with hyperconjugation. The elimination product, acetoxycyclohexene, was shown to be unstable under the reaction conditions. It affords cyclohexanone, which could be detected among the reaction products (6% from the unlabeled tresylate). Thus, this relatively large β effect could be ascribed to a partial rate-determining elimination in addition to hyperconjugation. Although the hydrogen participation cannot be precisely assessed,[23] an alternative rationalization based on hyperconjugation only is also conceivable. Shiner[16] reported β effects as high as 1.30 for cases where the dihedral angle between the C–D bond and the vacant p orbital is close to zero. In our particular case owing to the presence of an electron-withdrawing group a conformation favoring maximal C–H(D) hyperconjugation should be preferred[24] and the β effect could be even larger as to account entirely for the observed value of 1.34. However, the present set of experimental data does not allow us to distinguish between these two interpretations.

Experimental Section

Melting points are uncorrected. The progress of all reactions was followed by thin layer chromatography on silica gel. Infrared spectra were recorded on a Perkin-Elmer Infracord 137 spectrometer. For NMR spectra a Varian A-60 instrument was used. Chemical shifts are quoted in δ values against tetramethylsilane as internal standard. Mass spectra were taken on a Varian MAT CH7 mass spectrometer. Gas chromatography was performed on a Pye Unicam 104 instrument. A 5 ft × 0.25 in. column of 20% PEG 20M on 60–80 mesh Chromosorb W HP was used. Kinetic measurements were made on a Radiometer, Copenhagen, automatic titrator TTT2 with autoburette ABU11 and titrigraph SBR3. The deuterium content was determined by integration of the proton signals obtained on a Varian A-60, and the deuterium signals on a Varian HR-220 spectrometer and confirmed by mass spectrometry.

Materials. 2,2,2-Trifluoroethanesulfonyl chloride (tresyl chloride) (Willow Brook Laboratories, Inc., for synthetic purpose) and silica gel Merck (0.08–0.2 mm) for column chromatography were used. Lithium aluminum deuteride was Fluka A.G. (>99 atom % D).

***trans*-2-Acetoxycyclohexanol (2).** This material was prepared from *trans*-1,2-cyclohexanediol according to the method previously described.[9] The original procedure was modified insofar as isolation and purification were carried out by chromatography on a column of silica gel with ether–chloroform (4:1) as the eluent. In addition to **2** (31% yield) the corresponding diacetate (32%) was also obtained: ir (neat) 3500, 1740 cm^{-1}; NMR (CCl_4) δ 0.90–2.15 (m, 8 H), 1.97 (s, 3 H), 3.10 (s, 1 H), 3.17–3.64 (m, 1 H), 4.24–4.70 (m, 1 H).

***trans*-2-Acetoxycyclohexyl Tresylate (*trans*-1).** To a cooled (0 °C) solution of 550 mg (3.5 mmol) of *trans*-2-acetoxycyclohexanol and 430 mg (4.3 mmol) of triethylamine in 30 ml of dry dichloromethane, 680 mg (3.7 mmol) of tresyl chloride was added dropwise with stirring. The temperature of the reaction mixture was kept below 0 °C during the addition. The mixture was then washed with water followed by cold 10% sulfuric acid, water, saturated sodium bicarbonate, and saturated sodium chloride solution. After drying ($MgSO_4$) and removal of the solvent in vacuo, recrystallization from petroleum ether afforded 409 mg (38%) of pure product: mp 66–67 °C; ir (KBr) 1740, 1380, 1250, 1185, 1095, 930 cm^{-1}; NMR (CCl_4) δ 1.10–2.40 (m, 8 H), 1.98 (s, 3 H), 3.78 (q, 2 H, J = 9 Hz), 4.50–4.73 (m, 2 H).

Anal. Calcd for $C_{10}H_{15}F_3O_5S$: C, 42.35; H, 5.28. Found: C, 42.60; H, 5.39.

***cis*-2-Acetoxycyclohexanol (3).** This compound was prepared from *cis*-1,2-cyclohexanediol according to the same procedure[9] described above for the trans isomer, **2**. In addition to the corresponding diacetate (32%) 26% of the desired product was obtained: ir (neat) 3500, 1750 cm^{-1}; NMR (CCl_4) δ 1.10–2.15 (m, 8 H), 2.04 (s, 3 H), 3.65–3.94 (m, 1 H), 4.67–4.95 (m, 1 H).

***cis*-2-Acetoxycyclohexyl Tresylate (*cis*-1).** Following the same procedure described for the corresponding trans isomer, *trans*-1, 40% of pure product was obtained; mp 68–69 °C; ir (KBr)

1760, 1370, 1340, 1250, 1185, 1140, 1095, 1060, 985, 945, 920 cm^{-1}; NMR (CCl_4) δ 1.42–2.20 (m, 8 H), 2.01 (s, 3 H), 3.90 (q, 2 H, J = 9 Hz), 4.54–5.23 (m, 2 H).

***trans*-2-Hydroxycyclohexyl Tresylate (4).** *trans*-1,2-Cyclohexanediol (5.7 g, 49 mmol) and 3.0 g (30 mmol) of triethylamine were dissolved in 350 ml of dry dichloromethane and the solution cooled to −5 °C. Tresyl chloride (5.5 g, 25 mmol) was then added dropwise with stirring, keeping the temperature of the reaction mixture below 0 °C. The resulting solution was then washed with water followed by saturated sodium bicarbonate solution and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the crude product chromatographed on a column of silica gel with benzene–ether (4:1) yielding 3.7 g (57%) of pure product: mp 61–65 °C; ir (KBr) 3480, 1375, 1270, 1195, 1140, 1095, 980, 935 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.59 (m, 8 H), 2.50 (s, 1 H), 3.47–3.93 (m, 1 H), 4.18 (q, 2 H, J = 9 Hz), 4.47–4.85 (m, 1 H).

2-Oxocyclohexyl Tresylate (5). To a solution containing 400 mg (1.5 mmol) of 2-hydroxycyclohexyl tresylate in 15 ml of acetone, Jones reagent (CrO_3–H_2SO_4) was added with stirring at room temperature until the TLC control showed the absence of starting material (6 h). The reaction mixture was then diluted with 25 ml of ether and 20 ml of water, and the ethereal layer was separated, washed twice with water, and dried ($MgSO_4$). The evaporation of the solvent in vacuo left 330 mg (85%) of product which recrystallized from petroleum ether showed mp 88–90 °C; ir (KBr) 1730, 1390, 1280, 1260, 1190, 935 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.72 (m, 8 H), 4.27 (q, 2 H, J = 9 Hz), 5.00–5.40 (m, 1 H).

***cis*- and *trans*-2-Hydroxycyclohexyl-*2*-d_1 Tresylate (6, 7).** To a cooled (0 °C) solution of 600 mg (2.3 mmol) of 2-oxocyclohexyl tresylate in 25 ml of methanol, 50 mg (1.2 mmol) of sodium borodeuteride was added. After the reaction was complete, 100 ml of ether and 40 ml of water was added to the reaction mixture. The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo left 580 mg (96%) of a mixture of isomeric alcohols: ir (neat) 3600, 1380, 1325, 1255, 1180, 1140, 935 cm^{-1}.

The isomers were not separated at this stage but used as such in the next step.

***cis*- and *trans*-2-Acetoxycyclohexyl-*2*-d_1 Tresylate (*cis*-1βd, *trans*-1βd).** To a cooled (0 °C) solution of 580 mg of the mixture of *cis*- and *trans*-2-hydroxycyclohexyl-2-d_1 tresylate, dissolved in 15 ml of dry pyridine, excess of acetyl chloride (2.0 ml) was added dropwise, with stirring. After 6 h, 100 ml of ether and 20 g of crushed ice were added to the reaction mixture. The organic layer was separated, washed with cold 10% sulfuric acid followed by water, and dried ($MgSO_4$) and ether removed in vacuo. The resulting 596 mg of crude solid (99%) was purified by chromatography on a column of silica gel with benzene–ether (4:1) as the eluent.

The separation of isomers was achieved mechanically. After slow crystallization from petroleum ether two different types of crystals of convenient size were obtained. Careful separation with the aid of a microscope gave 312 mg of massive blocks (cis isomer, *cis*-βd) and 60 mg of fine clustered needles (trans isomer, *trans*-1βd) with the following characteristics. Cis isomer: mp 68–69 °C; ir (KBr) 1740, 1370, 1360, 1255, 1190, 1140, 1100, 970, 945, 925 cm^{-1}; NMR (CCl_4) δ 1.36–2.16 (m, 8 H), 1.98 (s, 3 H), 3.91 (q, 2 H, J = 9 Hz), 4.92–5.12 (m, 1 H). Trans isomer mp 66–67 °C; ir (KBr) 1740, 1370, 1250, 1185, 1145, 1095, 930 cm^{-1}; NMR (CCl_4) δ 1.14–2.43 (m, 8 H), 1.98 (s, 3 H), 3.87 (q, 2 H, J = 9 Hz), 4.43–4.81 (m, 1 H); deuterium content 0.85 atom D per molecule (NMR).

2-Hydroxycyclohexanone-*2*-*d* (9). To a suspension of 3.0 g (70 mmol) of lithium aluminum deuteride in 50 ml of dry ether, 11.2 g (100 mmol) of 1,2-cyclohexanedione was added at such a rate that gentle boiling was maintained. The resulting mixture was refluxed with stirring for 30 min, 15 ml of water was then added, and the precipitate was filtered and washed with ether. The aqueous layer of the filtrate was separated and extracted thoroughly with ether, the ethereal layers were combined and dried (Na_2SO_4) and ether was removed in vacuo. On standing for 24 h from 6.3 g of a crude oily product, 0.6 g of crystalline hemiketal 8 was filtered off and washed with ether. The oily residue was then chromatographed on a column of silica gel with ether–benzene (4:1) yielding 1.5 g of the solid dimer 8: mp 143–150 °C; ir (KBr) 3400, 1220, 1130, 1100, 985, 950, 860 cm^{-1}. As by-products 2.0 g of 1,2-cyclohexanediol and 1.1 g of a product whose identity was not examined were obtained.

On heating in a sealed tube under nitrogen to the melting point the dimeric product 8 was converted into the liquid monomer **9**, which was immediately used in the next step: ir (neat) 3500, 1710, 1100, 890 cm^{-1}.

2-Oxocyclohexyl-*1*-d_1 Tresylate (10). To a cooled (0 °C) solution of 1.5 g (13 mmol) of freshly prepared 2-hydroxycyclohexanone-2-d_1 and 1.5 g of triethylamine in 40 ml of dry dichloromethane, 2.4 g (13 mmol) of tresyl chloride was added dropwise with stirring during 15 min. Stirring was prolonged for 15 min, and the resulting solution was washed with water, followed by 10% sulfuric acid, water, saturated sodium bicarbonate, and saturated sodium chloride solution, and dried (Na_2SO_4). After the removal of solvent, chromatography on a column of silica gel with benzene–ether (7:3) as eluent gave 1.5 g (44%) of pure product: mp 89–90 °C; ir (KBr) 1715, 1390, 1330, 1260, 1190, 1140, 1095, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.65 (m, 8 H), 4.28 (q, J = 9 Hz), 5.00–5.40 (m, 1 H).

***cis*- and *trans*-2-Hydroxycyclohexyl-*1*-d_1 Tresylate (11, 12).** 2-Oxocyclohexyl-1-d_1 tresylate (1.3 g, 5 mmol) was reduced with 0.15 g (4 mmol) of sodium borohydride under the same conditions as described above for the preparation of isomeric alcohols **6** and **7**. The chromatography on a column of silica gel with benzene–ether (7:3) yielded 0.9 g (69%) of the mixture of isomeric alcohols **11** and **12** which was used as such in the next step.

***cis*- and *trans*-2-Acetoxycyclohexyl-*1*-d_1 Tresylate (*cis*-1αd, *trans*-1αd).** The mixture of *cis*- and *trans*-2-hydroxycyclohexyl-1-d_1 tresylate (0.9 g) was esterified with 3.0 ml of acetyl chloride in 20 ml of dry pyridine following the procedure described above for corresponding β-deuterated compounds *cis*-1βd and *trans*-1βd. After careful separation of the crystals 250 mg of the cis and 50 mg of the trans isomer were obtained. Cis isomer: ir (KBr) 1740, 1390, 1340, 1250, 1185, 1140, 1095, 1055, 925 cm^{-1}; NMR ($CDCl_3$) δ 1.37–2.15 (m, 8 H), 2.05 (s, 3 H), 3.97 (q, 2 H, J = 9 Hz), 4.73–5.17 (m, 1 H); deuterium content 0.70 atom D per molecule. Trans isomer: ir (KBr) 1740, 1380, 1250, 1180, 1145, 1090, 925 cm^{-1}; deuterium content 0.70 atom D per molecule.

1,4-Dioxa-6-oxospiro[4.5]decane (13). A solution of 10 g of 1,2-cyclohexanedione in 300 ml of benzene, an equimolar amount of 1,2-dihydroxyethane, and 100 mg of *p*-toluenesulfonic acid was heated at reflux for 8 h. Water was continuously separated. The resulting solution was washed with sodium hydroxide solution, and dried ($MgSO_4$) and the solvent evaporated in vacuo. Ten grams (62%) of a crude oily product was obtained. The crude product containing a certain amount of the diketal was used without further purification in the next step: ir (neat) 1740, 1200, 1100, 1028, 957, 905 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.05 (m, 6 H), 2.34–2.72 (m, 2 H), 3.94 (s, 4 H).

1,4-Dioxa-6-oxospiro[4.5]decane-*7,7*-d_2 (14). A reaction mixture containing 5 g (32 mmol) of the crude monoketal **13** and 20 mg of sodium deuteroxide in 50 ml of D_2O–dioxane (1:1 mixture) was heated at 50 °C for 10 h. Solvent was then removed in vacuo and the oily residue was treated twice as described before. After final removal of the solvent 50 ml of benzene was added to the residue, and the resulting solution was washed with 5 × 5 ml of D_2O. After drying ($MgSO_4$) and the removal of benzene in vacuo 4.5 g (89%) of an oily product was obtained: ir (neat) 2220, 2130, 1735, 1190, 1100, 1050, 1030, 955 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.05 (m, 6 H), 3.92 (s, 4 H); deuterium content better than 1.90 atoms D per molecule (by ^1H NMR).

1,4-Dioxa-6-hydroxyspiro[4.5]decane-*7,7*-d_2 (15). To a suspension of 540 mg (14 mmol) of lithium aluminum hydride in 60 ml of dry ether, 4.5 g (28 mmol) of crude ketone **14** dissolved in 5 ml of ether was added dropwise. Then 0.6 ml of water followed by 0.6 ml of 15% sodium hydroxide solution and 2 ml of water were added to the reaction mixture. The inorganic precipitate was filtered off, the ether layer separated, and the water layer extracted with ether. The combined ethereal extracts were dried ($MgSO_4$), ether removed in vacuo, and the crude product chromatographed on silica gel with benzene–ether (1:1); 2.9 g (64%) of pure oily product was obtained, ir (neat) 3140, 2220, 2130, 1165, 1100, 1030, 955, 985 cm^{-1}.

2-Hydroxycyclohexanone-*3,3*-d_2 (16). Ketal **15** (1.8 g) was dissolved in 15 ml of acetone, 15 ml of 20% sulfuric acid was added, and the resulting solution kept at 50 °C for 30 min. Acetone was then removed in vacuo and the residual aqueous solution extracted with dichloromethane (4 × 25 ml). The combined extracts were washed with sodium bicarbonate solution followed by water and dried ($MgSO_4$) and the solvent was evaporated in vacuo to a volume of ca. 40 ml. Complete removal of solvent was avoided because it causes the formation of the dimeric product **8**. The identity of the product was checked by TLC using the corresponding nondeuterated compound as a standard.

2-Oxocyclohexyl-6,6-d_2 Tresylate (17). To a cooled (0 °C) dichloromethane solution of the keto alcohol **16** from the previous step an equimolar amount of dry pyridine was added calculated on the basis of a 100% yield in the preceding ketal hydrolysis. An equimolar amount of tresyl chloride was then added dropwise with stirring. Isolation and purification as described for compound **10** afforded 1.1 g of crystalline product: ir (KBr) 1740, 1395, 1335, 1265, 1190, 1020, 935, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.75 (m, 6 H), 4.25 (q, 2 H, J = 9 Hz), 5.17 (s, 1 H).

***cis*- and *trans*-2-Hydroxycyclohexyl-6,6-d_2 Tresylate (18, 19).** Using the procedure described for the preparation of compounds **11** and **12** (Scheme III), 1.1 g of keto tresylate **17** gave 0.8 g (73%) of a mixture of isomeric alcohols, which was used without further purification in the next step.

***cis*- and *trans*-2-Acetoxycyclohexyl-6,6-d_2 Tresylate (*cis*-1$\beta'd_2$, *trans*-1$\beta'd_2$).** Applying the same method of preparation and separation as described for corresponding compounds *cis*-1αd and *trans*-1αd in Scheme III, 293 mg (32%) of pure cis and 70 mg (8%) of trans product was obtained. Cis isomer: ir (KBr) 2220, 2130, 1780, 1390, 1250, 1175, 1145, 1080, 915 cm^{-1}; NMR ($CDCl_3$) δ 1.15–2.00 (m, 6 H), 2.02 (s, 3 H), 3.92 (q, 2 H, J = 9 Hz), 4.65–5.25 (m, 1 H); deuterium content 1.95 atoms D per molecule (NMR). Trans isomer: ir (KBr) 2220, 2130, 1745, 1380, 1250, 1185, 1145, 1095, 930 cm^{-1}; NMR ($CDCl_3$) δ 1.20–2.00 (m, 6 H), 2.00 (s, 3 H), 3.85 (q, 2 H, J = 9 Hz), 4.45–4.80 (m, 1 H); deuterium content 1.95 atoms D per molecule (NMR).

***trans*-2-Hydroxycyclohexyl 2,2,2-Trifluoroethyl Ether (20).** A solution of 0.98 g (10 mmol) of cyclohexene oxide in 30 ml of 2,2,2-trifluoroethanol and one drop of sulfuric acid was heated to reflux for 1 h. Barium carbonate was added to the cooled reaction mixture to neutralize the acid and the resulting precipitate filtered off. The filtrate was concentrated in vacuo and the residue chromatographed on column of silica gel with benzene–ether (4:1) yielding 0.4 g (50%) of oil: ir (neat) 3460, 1280, 1180, 1160, 1120, 970 cm^{-1}.

***trans*-2-Acetoxycyclohexyl 2,2,2-Trifluoroethyl Ether (21).** *trans*-2-Hydroxycyclohexyl trifluoroethyl ether (197 mg, 0.1 mmol) in 10 ml of dry pyridine was treated with excess of acetyl chloride following the procedure for preparation of *cis*-1βd and *trans*-1βd described above. The chromatography on a column of silica gel with benzene–ether (9:1) as the eluent afforded 150 mg (63%) of pure oil: ir (neat) 1745, 1280, 1245, 1160, 1125, 1060, 1045, 974 cm^{-1}; NMR (CCl_4) δ 1.77–2.18 (m, 8 H), 1.97 (s, 3 H), 3.10–3.58 (m, 1 H), 3.85 (q, 2 H, J = 9 Hz), 4.43–4.98 (m, 1 H). A small amount of the corresponding cis ether was also isolated and characterized by ir. It was used as a standard in the GLC analysis of solvolysis products.

Acetoxycyclohexene. This compound was prepared from cyclohexanol and acetic anhydride according to the published procedure.[25]

Kinetic Measurements. 2,2,2-Trifluoroethanol, 97 wt % (Fluka), was used as solvent in solvolyses. Measurements of the titrimetric rates for the trans derivatives *trans*-**1**, *trans*-1βd, *trans*-1αd, and *trans*-1$\beta'd_2$ were carried out by means of a pH-Stat Radiometer, Copenhagen, TTT2 titrator with ABU11 autoburette and SBR3 recorder.

The titrimetric cell with solvent was allowed to stabilize at the desired temperature (55 °C) prior to addition of substrates. The concentration of substrate was 6–7 mg/15 ml of solvent in all experiments. The titration solution was 0.02 N sodium hydroxide in 97 wt % TFE.

Six kinetic measurements were performed for each compound alterating the solvolysis of labeled and unlabeled substance.

Rate measurements for cis tresylates *cis*-**1**, *cis*-1βd, *cis*-1αd, and *cis*-1$\beta'd_2$ were accomplished by the usual ampule technique at 93° using 6 mg of substrate, 2 equiv of 2,6-lutidine, and 5 ml of solvent (97% TFE) in each ampule. The titration was accomplished potentiometrically with 0.02 N sulfuric acid as titration solution.

Rate data were evaluated by a nonlinear least-square sum-fitting program.

Product Studies. *trans*-2-Acetoxycyclohexyl tresylate (470 mg) in 180 ml of 97 wt % trifluoroethanol was solvolyzed at 55° under the same conditions as in the kinetic runs for at least 8 half-lives. GLC analysis showed only one product with identical retention time with *cis*-2-acetoxycyclohexanol. After dilution of the reaction mixture with water and subsequent ether extraction, the solvolysis product was isolated and identified as 2-acetoxycyclohexanol by ir spectroscopy.

cis-2-Acetoxycyclohexyl tresylate (608 mg) was solvolyzed in 130 ml of 97 wt % trifluoroethanol in the presence of 321 mg of 2,6-lutidine in sealed ampules at 93 °C. The products were identified by GLC and the major products isolated by column chromatography over silica gel and identified as *trans*-2-acetoxycyclohexyl trifluoroethyl ether (28.4%) by ir, NMR, and comparison with authentic samples. By separate experiments the stability of all products under the solvolytic conditions was determined. With the exception of acetoxycyclohexane all were found to be stable.

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Registry No.—*trans*-**1**, 57573-63-4; *cis*-**1**, 57573-64-5; *trans*-1d, 57573-65-6; *cis*-1d, 57573-66-7; *trans*-1βd, 57573-67-8; *cis*-1βd, 57573-68-9; *trans*-1$\beta'd_2$, 57573-69-0; *cis*-1$\beta'd_2$, 57573-70-3; **2**, 20520-69-8; **3**, 13858-62-3; **4**, 57573-71-4; **5**, 57573-72-5; **6**, 57573-73-6; **7**, 57573-74-7; **8**, 57573-75-8; **9**, 57573-76-9; **10**, 57573-77-0; **11**, 57573-78-1; **12**, 57573-79-2; **13**, 4746-96-7; **14**, 57573-80-5; **15**, 57573-81-6; **16**, 57573-82-7; **17**, 57573-83-8; **18**, 57573-84-9; **19**, 57573-85-0; **20**, 57573-86-1; **21**, 57573-87-2; *trans*-1,2-cyclohexanediol, 1460-57-7; tresyl chloride, 1648-99-3; *cis*-1,2-cyclohexanediol, 1792-81-0; 1,2-cyclohexanedione, 765-87-7; 1,2-dihydroxyethane, 107-21-1; cyclohexene oxide, 286-20-4; trifluoroethanol, 75-89-8.

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Sulfinic Acid Catalyzed Isomerization of Olefins

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Arenesulfinic acids catalyze the cis–trans equilibration of disubstituted olefins in high yield and without double bond migration, as evidenced by studies of the reaction of various sulfinic acids with methyl 9-octadecenoate and 4-octene. Equilibrium is attained within 15 min in refluxing dioxane at the lowest catalyst level investigated. None of the known decomposition products of sulfinic acids, including sulfinyl sulfones, appears to be responsible for the isomerization. Sulfinyl sulfones, which are formed from sulfinic acids in the initial step of the decomposition process, also catalyze the isomerization, but at a slower rate than the sulfinic acids.

Chemists have long sought mild, efficient methods for the conversion of naturally occurring cis unsaturated fatty acids to the trans isomers, and for the equilibration of isolated double bonds in general.[1] Most catalysts suffer from some disadvantage, such as toxicity, a high temperature requirement, or double bond migration. Probably the mildest and most convenient catalyst developed is nitrous acid.[1] More recently, isomerization by photochemically generated thiyl radicals[2–4] and by mercaptans in aqueous solution have been developed.[5] While in search of a new and more convenient method, we encountered two references to the use of *p*-toluenesulfinic acid for this purpose. During a study of reduction of olefins by diimide, generated by thermal decomposition of *p*-toluenesulfonylhydrazine, Garbisch et al. noted that the *p*-toluenesulfinic acid by-product of the decomposition caused the isomerization of the double bond, without specifying the nature of the isomerization.[6] It was found that the isomerization could be prevented by the addition of triethylamine to the reaction, presumably by neutralization of the sulfinic acid. Nozaki et al. found that when methyl oleate was treated with an excess of *p*-toluenesulfinic acid for 7 h in dioxane at 90 °C, an "equilibrium" mixture, containing 55% of methyl elaidate, the trans isomer, was obtained in 60% yield.[7] We chose to examine this process in more detail, to answer such questions as: Is the process catalytic, and if so, what is the nature of the catalytic species? Is thermodynamic equilibrium actually attained, since under Nozaki's conditions methyl elaidate should comprise about 75% of the oleate–elaidate mixture at equilibrium? Does double bond migration occur? And are there more favorable conditions under which the isomerization can be effected? This paper presents an initial examination which answers some of the above questions and serves to eliminate some of the more obvious candidates for the species responsible for the isomerization.

Results and Discussion

Treatment of a solution of either methyl oleate or methyl elaidate in dioxane at reflux for 2 h with 10 mol % of *p*-toluenesulfinic acid gave an equilibrium mixture comprised of 76% of the trans isomer. The catalytic nature of the process is shown in Table I, which shows that equilibration is possible with varying catalyst–olefin ratios. Gas chromatographic analysis showed that in each instance equilibrium was obtained in less than 15 min. The incomplete equilibration observed at the lowest ratio examined suggests that the catalytic species is itself consumed by some competing process.

The influence of sulfinic acid catalyst structure on the isomerization is shown in Table II. It is apparent that catalytic activity is relatively independent of the structure of the sulfinic acid. The low degree of isomerization with *o*-nitrobenzenesulfinic acid is reproducible, but as yet unexplained.

Table I. Isomerization of Methyl Oleate with p-Toluenesulfinic Acid[a]

Catalyst ratio[b]	% trans
1.48	78.7
0.148	81.0
0.0148	78.1
0.0080	69.1

[a] 2 h at reflux, in dioxane, 0.085 M. [b] Molar equivalents of sulfinic acid per mole of methyl oleate.

Table II. Effect of Sulfinic Acid Structure on Isomerization of Methyl Oleate[a]

Registry no.	Sulfinic acid	% yield[b]	% trans
618-41-7	Benzene-	91	80.8
536-57-2	*p*-Toluene-	88	80.0
100-03-8	*p*-Chlorobenzene-	95	81.0
1195-33-1	*p*-Bromobenzene-	91	79.3
1709-60-0	*p*-Methoxybenzene-	91	79.6
1199-67-3	*o*-Nitrobenzene-	93	26.6

[a] 10 mol % catalyst, refluxing dioxane, 3 h, 0.43 *M*. [b] Distilled product.

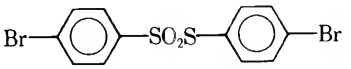
The absence of double bond migration in the substrate was demonstrated by oxidation of the product from the *p*-bromobenzenesulfinic acid catalyzed reaction with the permanganate–periodate reagent.[8] Esterification of the resulting carboxylic acids with diazomethane followed by gas chromatographic analysis showed that less than 0.5% migration to the C_8 or C_{10} positions had occurred.

With the preliminary questions concerning the reaction thus answered, we began attempts to determine the nature of the catalytic species responsible for the isomerization. Both methyl *p*-toluenesulfinate and the sodium salt proved to be ineffective as catalysts under the conditions used in Table II and the oleate proved to be stable in refluxing dioxane in the absence of added materials. This suggests that the free sulfinic acid is required, but does not identify the catalytic species. Aromatic sulfinic acids are known to decompose thermally by disproportionation to sulfonic acid and thiolsulfonate:[9]

$$3ArSO_2H \rightarrow ArSO_3H + ArSO_2SAr + H_2O$$

Nozaki had noted that neither *p*-toluenesulfonic acid nor the neutral products of the decomposition of *p*-toluenesulfinic acid caused the isomerization of methyl oleate.[7] We confirmed this observation with regard to *p*-toluenesulfonic acid. However, 4,4′-dibromodiphenyl thiolsulfonate (1) did cause isomerization of methyl oleate in refluxing dioxane, but at a much slower rate than that shown by the sulfinic acid. Thus, equilibration of methyl oleate requires 5 h

in the presence of 0.1 equiv of **1**, compared with less than 15 min with the sulfinic acids.



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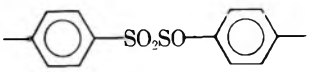
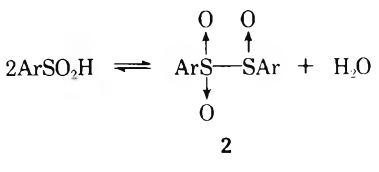


3

Another attractive hypothesis is that the radical intermediates in the disproportionation of the sulfinic acid are responsible for the olefin isomerization. Kice has shown, in a detailed study of this disproportionation,[10] that arenesulfinic acids form sulfinyl sulfones, **2**, which cleave thermally to sulfinyl and sulfonyl radicals:



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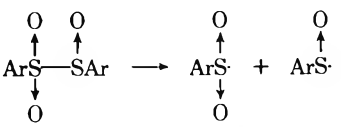

Recombination and further reactions can also generate the arylthiyl radical, ArS·, as well. All of these radicals are candidates for the species responsible for the isomerization.

In an attempt to gain some information concerning this point, we obtained data for the initial rates of isomerization of *cis*-4-octene in the presence of *p*-toluenesulfinic acid and the sulfinyl sulfone **3**. Both reactions proved to be too fast at the reflux temperature of dioxane to conveniently obtain more than two data points before equilibrium was reached. That equilibrium was in fact obtained was determined by carrying out the isomerization of both *cis*- and *trans*-4-octene with both catalysts, giving in each case 76% trans isomer. The reaction with *cis*-4-octene was more conveniently studied at 70 °C, at which temperature the isomerization was found to follow good first-order kinetics for isomerization to about 20% trans isomer. The first-order rate constants for the disappearance of *cis*-4-octene in the presence of 0.1 molar equiv of either **3** or *p*-toluenesulfinic acid are shown in Table III.

Table III[a]

Catalyst	$k_1 \times 10^4$, s^{-1}
p-Toluenesulfinic acid	9.3 ± 0.5
p-Toluenesulfinyl-*p*-toluene sulfone (**3**)	0.58 ± 0.01

[a] 70 ± 1 °C, 0.107 M in *cis*-4-octene, 0.0107 M in catalyst. Average of three runs in anhydrous dioxane.

Kice has shown that an equilibrium concentration of a few percent of the sulfinyl sulfone exists in solutions of the sulfinic acid, but that the rate of attainment of this equilibrium is very slow in the absence of strong acids. In addition, the rate of thermal cleavage of the sulfinyl sulfone is independent of the presence of sulfinic acid, and represents the rate-determining step in the sulfinic acid disproportionation reaction. Therefore, while the sulfinyl sulfone does promote isomerization of olefins at a moderate rate, presumably via the radical cleavage products, these radicals do not represent major catalytic species when sulfinic acid is used. The rapid and clean isomerization observed with the sulfinic acid must be due to the action of the acid itself or to some as yet unobserved species which is formed in competition with or prior to sulfinyl sulfone.

The nature of the catalytic species must await more thorough kinetic studies and complete product analysis to determine the fate of the sulfinic acid. An initial investigation of the latter point showed the presence of a multitude of sulfur-containing products, none of which has been identified. Whatever their nature, the reaction represents a convenient method for the equilibration of olefins in high yield and excellent purity, and should find application as a synthetic method in a variety of substrates.

Experimental Section

Materials. Methyl oleate was obtained by esterification of oleic acid which had been purified by urea adduction to remove saturated acids. Gas chromatographic analysis indicated 95–98% purity. Methyl elaidate was obtained from Applied Science Laboratories. Benzenesulfinic acid and *p*-toluenesulfinic acid were obtained by acidification of aqueous solutions of the commercially available sodium salts with HCl. The other sulfinic acids were obtained by reduction of the sulfonyl chlorides with Na_2SO_3.[9] Recrystallization gave in each case material whose melting point was in good agreement with that cited in ref 9. *trans*-4-Octene was purchased from Aldrich and used as is. *cis*-4-Octene was prepared by reduction of 4-octyne with Pd/$BaSO_4$ catalyst poisoned with quinoline. GLC analysis showed the presence of 3.5% *trans*-4-octene.

Analytical Procedures. Melting points were determined on a micro hot stage and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 instrument as mulls in mineral oil or in CH_2Cl_2 solution. High-resolution mass spectra were determined with an Atlas SM-1 spectrometer. GLC analyses for methyl oleate–methyl elaidate reactions were performed at 180 °C on a 150 ft × 0.01 in. stainless steel column coated with polyphenyl ether. The instrument used was a Perkin-Elmer 126 with flame ionization detectors. GLC analyses for the 4-octene isomers were carried out at 50 °C on a 20 ft × 0.25 in. stainless steel column packed with 20% β,β′-oxydipropionitrile on Gas Chrom P. The instrument used was a Varian Aerograph Model 202B with thermal conductivity detectors.

Isomerization of Methyl Oleate with Varying Amounts of *p*-Toluenesulfinic Acid. To a solution of 1.0 g of methyl oleate in 40 ml of dry dioxane was added 0.78 g of *p*-toluenesulfinic acid. The system was flushed with argon and heated to reflux for 1 h. After cooling, the solution was diluted with pentane and extracted with 1 N NaOH solution, then washed twice with saturated sodium chloride solution. The pentane solution was dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. GLC analysis of a pentane solution of the residue on the PPE column showed only methyl oleate and methyl elaidate in a ratio of 21.3:78.7. Reaction of the same amount of methyl oleate with *p*-toluenesulfinic acid at lower levels gave the results shown in Table I.

Equilibration Studies. Methyl oleate and methyl elaidate (0.20 ml) were treated separately with 2.87 ml of 0.0216 M *p*-toluenesulfinic acid in dioxane at reflux for 2 h. Duplicate runs with each ester gave averages of 75.2 and 76.0% elaidate, respectively, by quantitative infrared analysis.

Preparative Scale Isomerization of Methyl Oleate. A solution of 0.068 mol (20 g) of methyl oleate and 0.0068 mol of a sulfinic acid in 135 ml of dry dioxane was heated to reflux under argon for 3 h. After work-up similar to that already described, vacuum distillation gave high yields of methyl oleate–elaidate mixtures with compositions given in Table II as determined by GLC analysis. TLC of samples of distilled products at high load levels revealed the presence of trace impurities, estimated to be on the order of ≤0.1%.

Preparation of 4-Bromobenzenethiol 4′-Bromobenzenesulfonate (1). A solution of 0.76 g of *p*-bromobenzenesulfinic acid in 400 ml of toluene was refluxed for 1 h. The cooled solution was washed with 1 N NaOH and saturated sodium chloride solution and dried over $MgSO_4$. Chromatography of the residue after removal of solvent was carried out on 20 g of silica gel. Elution with ether gave 52.6 mg of crystals, mp 134–137 °C. Recrystallization from ether–pentane raised the melting point to 175–178 °C. TLC of this material on silica gel showed a single spot with ir (mull) λ_{max} 6.40, 7.52, 8.77, 9.40, and 9.94 μ, NMR signals at τ 2.7–3.0 ($CDCl_3$), and molecular ions at *m/e* 406, 408, and 410 in accord with the molecular formula $C_{12}H_8S_2O_2Br_2$. In addition, the mass

spectrum showed major fragment ions in accord with cleavages of the C–S and S–S bonds in structure 1.

Isomerization of Methyl Oleate with Thiolsulfonate (1). A solution of 1.0 g (0.0034 mol) of methyl oleate and 0.139 g (0.00034 mol) of 1 in 40 ml of dioxane was heated to reflux for a total of 5 h. Periodic withdrawal of 5-ml aliquots, normal work-up, and GLC analysis gave the following results, with time in minutes and percent trans isomer: 61 (51), 126 (60), 178 (73), 249 (77), and 306 (77.5).

Isomerization of *cis*- and *trans*-4-Octene with 3 and *p*-Toluenesulfinic Acid. The sulfinyl sulfone 3 was prepared as previously described and gave an infrared spectrum identical with that published.[11]

For the kinetic runs, 5.0 ml of a 0.0214 M solution of 3 or the sulfinic acid in dry dioxane was added to 5.0 ml of 0.214 M *cis*-4-octene in dioxane in a round-bottom three-neck flask which had been oven dried and flushed with dry nitrogen. The octene solution was also 0.10 M in decane for use as an internal standard. The flask was immersed in an oil bath held at 70 ± 1 °C with a relay, and aliquots were withdrawn periodically via syringe through a rubber cap. After dilution with pentane and washing once with 1 N NaOH and twice with water, gas chromatographic analysis gave the amount of isomerization with an accuracy of ±0.5%. The averages of the least-squares first-order plots of three runs, taken up to 20–30% isomerization, were determined to give the initial rate constants shown in Table III. Gas chromatographically determined yields were 93% for the sulfinic acid process at equilibrium but were lower when the sulfinyl sulfone was used. A blank reaction carried out in the absence of either isomerization reagent showed no trans isomer formation after 20 h.

Registry No.—1, 3347-03-3; 3, 788-86-3; methyl oleate, 112-62-9; methyl elaidate, 1937-62-8; toluene, 108-88-3; *cis*-4-octene, 7642-15-1; *trans*-4-octene, 14850-23-8.

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Linear Carboxylic Acid Esters from α Olefins. I. Catalysis by Homogeneous Platinum Complexes

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Ligand-stabilized platinum(II)–Group 4B metal halide complexes have been found to catalyze the homogeneous carbonylation of α olefins to carboxylic acids and esters, with up to 98 mol % selectivity to the linear ester. Preferred catalysts include $[(C_6H_5)_3As]_2PtCl_2$–$SnCl_2$, $[(C_6H_5)_2ClAs]_2PtCl_2$–$SnCl_2$, and $[(C_6H_5O)_3P]_2PtCl_2$–$SnCl_2$. The activity of each of these regioselective catalysts is highly sensitive to changes in coordinated ligand structure. The effects of catalyst and olefin composition, the nature of the nucleophilic coreactant, and other experimental variables upon both the activity and selectivity of the platinum have been examined, and are discussed in relation to the mode of this catalysis.

Carbonylation, the addition of CO to unsaturated compounds to yield carboxylic acid derivatives, may be catalyzed by a variety of soluble metal carbonyl species, including those of nickel, cobalt, iron, rhodium, ruthenium, palladium, and platinum.[1–8] α-Olefin carbonylation, as catalyzed by Reppe-type nickel and cobalt catalysts, is characterized by (a) the production of large quantities of branched, as well as linear, acid derivatives (eq 1),[3,5–7] (b) the importance of competing olefin polymerization, isomerization, and reduction reactions, and (c) severe operating conditions.[2] More recently, improved palladium catalysts have been found active under milder conditions where competing side reactions are of lesser importance,[4,9] and normal esters predominate.[10,11] Linear carboxylic acid esters have also been prepared in 67–85% selectivity with the H_2PtCl_6–$SnCl_2$ couple.[12,13]

$$\mathrm{RCH{=}CH + CO + R'OH} \rightarrow \mathrm{RCH_2CH_2COOR'} \quad (1a)$$

$$\mathrm{RCH{=}CH + CO + R'OH} \rightarrow \mathrm{RCHCOOR'\ (CH_3)} \quad (1b)$$

As part of a program to develop new routes to linear carboxylic acid derivatives, we report here the use of certain ligand-stabilized platinum(II)–Group 4B metal halide complexes as catalysts for the highly selective carbonylation of α olefins to linear carboxylic acid esters.[14]

Results

Effect of Platinum Catalyst Structure. In multistep reaction sequences such as carbonylation, modification of the catalyst metal center by changes in coordinated ligand structure may dramatically affect the activity and stability of the catalyst, the selectivity to straight-chain products, and competing side reactions.[2,4,8,9,15,16] In this work, a broad range of ligand-stabilized platinum(II) complexes in combination with Group 4B metal halide cocatalysts have been screened for carbonylation activity, and methyl octanoate synthesis from 1-heptene has been selected as the model reaction (see Tables I and II).

The first distinguishing feature of this class of catalysts is their ability to produce linear acid esters, such as methyl octanoate, in at least 90 mol % selectivity. This selectivity is consistently higher than has been reported previously,[1–10,12,13] even for related palladium bimetallic catalysts.[17] The highest selectivity to methyl octanoate achieved here (98 mol %) is with dichlorobis(triphenyl phosphite)platinum(II)–tin(II) chloride (expt 5). The highest yield of meth-

Table I. 1-Heptene Carbonylation Catalyzed by Various Platinum(II) Complexes I[a]

Expt	Composition of platinum complex	1-Heptene conversion, mol %	Yield of 2,3-heptenes, mol %	Methyl octanoate Yield, mol %[b]	Methyl octanoate Selectivity, mol %[c]
1	$[(C_6H_5)_3As]_2PtCl_2-10SnCl_2$	95	4.2	86	93
2	$[(C_6H_5)_2ClAs]_2PtCl_2$[d]$-10SnCl_2$	89	19	59	92
3	(DIARS)$PtCl_2$[e]$-10SnCl_2$	28	4.7	21	91
4	$[(C_6H_5)_3As]_2PtCl_2-10SnCl_2-5As(C_6H_5)_3$	91	18	61	91
5	$[(C_6H_5O)_3P]_2PtCl_2-10SnCl_2$	34	<2	28	98
6	$[(p\text{-}ClC_6H_4)_3P]_2PtCl_2-10SnCl_2$	9.3	<2	6.1	95
7	$[(C_6H_5)_3P]_2PtCl_2-10SnCl_2$	21	16	3.4	91
8	$[(p\text{-}CH_3OC_6H_4)_3P]_2PtCl_2-10SnCl_2$	15	8.7	0.8	94
9	$[C_6H_5(CH_3)_2P]_2PtCl_2-10SnCl_2$	3.5	<2	None	
10	$[(C_6H_5)_3Sb]_2PtCl_2-10SnCl_2$	12	<2	3.0	95
11	$[(C_6H_5)_2S]_2PtCl_2-10SnCl_2$	72	8.5	52	92
12	(1,10-PHEN)$PtCl_2$[g]$-10SnCl_2$	41	8.0	32	96
13	$[(C_6H_5)_3P]_4Pt-10SnCl_2$	3.5[f]	<2	2.2	90

[a] Run conditions: [1-heptene], 0.52 M; [Pt]:[1-heptene]:[methanol] 1:100:740; 240 atm, 80°C, 6 h. [b] Methyl octanoate yield based on 1-heptene charged. [c] Selectivity calculated basis: methyl octanoate yield/total methyl C_8 acid esters. [d] Prepared in situ. [e] DIARS, $(C_6H_5)_2AsCH_2CH_2As(C_6H_5)_2$. [f] Run at 105 °C, no reaction at 80 °C. [g] 1,10-PHEN, 1,10-phenanthroline.

Table II. 1-Heptene Carbonylation Catalyzed by Various Platinum(II) Complexes II[a]

Expt	Composition of platinum complex	1-Heptene conversion, mol %	Yield of 2,3-heptenes, mol %	Methyl octanoate Yield, mol %	Methyl octanoate Selectivity, mol %
14	$[(C_6H_5)_3As]_2PtCl_2-10SnCl_2$	95	4.2	86	93
15	$[(C_6H_5)_3As]_2PtCl_2-10GeCl_2$[b]	3.6	<2	1.0	94
16	$[(C_6H_5)_3As]_2PtCl_2-10PbCl_2$	2.0	<2	1.6	90
17	$[(C_6H_5)_3As]_2PtCl_2-10SbCl_3$	2.6	<2	None	
18	$[(C_6H_5)_3As]_2PtCl_2-10SnCl_4$	52	<3	44	92
19	$[(C_6H_5)_3As]_2PtI_2-10SnI_2$	7.0	<2	6.5	>90
20	$[(C_6H_5)_3As]_2PtCl_2$	<2	<2	None	
21	$[(C_6H_5)_3As]_2Pt(CN)_2$	<2	<2	None	
22	$[(C_6H_5)_3As]_2PtCl_2-30SnCl_2$	64	8.6	35	92
23	$[(C_6H_5)_3As]_2PtCl_2-5SnCl_2$	63	5.9	56	92
24	$[(C_6H_5)_3As]_2PtCl_2-1SnCl_2$	33	6.9	22	94

[a] Run conditions: [1-heptene], 0.52 M; [Pt]:[1-heptene]:[methanol] 1:100:740, 240 atm, 80°C, 6 h. [b] Added as $CsGeCl_3$.

yl octanoate (86 mol %) is with dichlorobis(triphenylarsine)-platinum(II)–tin(II) chloride (expt 1).

The nature of the Group 5B or 6B donor ligands (Table I) and the Group 4B metal halides (Table II) generally has a marked effect upon the platinum carbonylation activity, but a far smaller effect upon the selectivity to the linear esters, and the degree of competing double bond migration. While no simple correlation has been found, or even anticipated, between the performance of the platinum(II)–tin(II) chloride complexes and either the steric[18] or electron donor–acceptor properties[19] of the coordinated Group 5B and 6B ligands, generally improved yields of linear ester have been obtained with strong π-acceptor ligands of low basicity such as triphenylarsine and triphenyl phosphite. In a homologous series of platinum–phosphine complexes (expt 5–9), decreasing basicity of the coordinated ligands[19] leads to increasing yields of ester in the order

$$P(CH_3)_2C_6H_5 < P(p\text{-}CH_3OC_6H_4)_3 < P(C_6H_5)_3 < P(p\text{-}ClC_6H_4)_3 < P(OC_6H_5)_3 \quad (2)$$

with complexes of strongly basic ligands, such as $P(n\text{-}C_4H_9)_3$ and $P(CH_3)_2(C_6H_5)$, being inactive under these conditions. For ligands of different donor atoms, however, the observed trends (e.g., eq 3) may best be rationalized in terms of competing steric and electronic factors.[20,21]

$$P(C_6H_5)_3 \approx Sb(C_6H_5)_3 < S(C_6H_5)_2 < AsCl(C_6H_5)_2 < As(C_6H_5)_3 \quad (3)$$

Analogous platinum(0) complexes, e.g., $(Ph_3P)_4Pt-SnCl_2$, expt 13, provide poor catalyst precursors. Complexes of bidentate ligands such as bis(diphenylarsino)ethane and 1,10-phenanthroline show improved thermal stability, but this is accompanied by a marked reduction in activity that may be attributed either to the limited solubility of these complexes, or the increased difficulty in ligand substitution.

Dichlorobis(triphenylarsine)platinum(II), in the absence of a Group 4B metal halide cocatalyst, fails to carbonylate α olefins (Table II, expt 20). Significant yields of methyl octanoate are afforded, however, with metal chloride cocatalysts such as tin(II) chloride, tin(IV) chloride, and lead(II) chloride; the highest yields of linear ester are obtained with tin(II) chloride (expt 14) at Sn:Pt mole ratios of around 10 (expt 14, 22–24). Similarly, among different tin(II) halides, $SnCl_2$ is more effective than SnI_2. This order of effectiveness (eq 4 and 5) parallels that found for the bimetallic hydroformylation catalysts $(R_3P)_2PtX_2$-MX_2[22], and the order of stability of platinum–Group 4B metal bonds.[23,24] It should be noted, nevertheless, that no carbonylation is evident when $SnCl_3^-$ is replaced by other powerful π-acceptor ligands[25,26] such as antimony trichloride, cyanide ion, and CO itself.

$$GeCl_2 < SnCl_2 > PbCl_2 \quad (4)$$

$$SnCl_2 > SnI_2 \quad (5)$$

Table III. Olefin Carbonylation Catalyzed by Solutions of $[(C_6H_5)_3As)]_2PtCl_2$–$SnCl_2$[a]

Expt	Alkene	Registry no.	Initial mole ratio alkene/Pt	Reaction time, min	Alkene conversion, %	Major carbonylation products: Identity	Major carbonylation products: Selectivity, mol %
25	Propylene	115-07-1	100	360	30	Methyl butyrate	76
26	1-Heptene	592-76-7	100	360	51	Methyl octanoate	95
27	1-Tetradecene	1120-36-1	100	360	34	Methyl pentadecanoate	88
28	1-Eicosene	3452-07-1	50	300	29	Methyl heneicosanoate	>95
29	3-Methyl-1-pentene	760-20-3	50	480	74	Methyl 4-methylhexanoate	>99
30	4-Methyl-1-pentene	691-37-2	50	360	50	Methyl 5-methylhexanoate	97
31	2,4,4-Trimethyl-1-pentene	107-39-1	50	360	No reaction		
32	Cyclohexene	110-83-8	50	360	No reaction		
33	2-Decene	6816-17-7	100	180	No reaction		
34	1-Heptene		100	180	41	Methyl octanoate	92
	trans-2-Heptene	14686-13-6	100	180	<1	None	—
	trans-5-Decene	7433-56-9	50	180	<1	None	—

[a] Run conditions: 80° C, 140 atm, excess methanol.

Table IV. 1-Heptene Carbonylation Catalyzed by Solutions of $[(C_6H_5)_3)As]_2PtCl_2$–$SnCl_2$. Effect of Changes in Nucleophilic Coreactant

Expt	Nucleophilic coreactant	Heptene conversion, mol %	Major carbonylation product: Identity	Major carbonylation product: Selectivity, mol %	Major carbonylation product: Yield, mol %
35	Ethanethiol	5.1	Ethyl thioloctanoate	95	2.8
36	Water	43	Octanoic acid[b]	91	30
37	2-Chloroethanol	79	2-Chloroethyl octanoate	90	65
38	2-Propanol	15	Isopropyl octanoate	94	12
39	1-Octanol	67	Octyl octanoate	94	60
40	Methanol	91	Methyl octanoate	93	86
41	Phenol	52	Phenyl octanoate	93	25

[a] Run conditions: [1-heptene], 0.47 → 0.59 M, [Pt]:[1-heptene]:[ROH] 1:100:300, 240 atm, 80° C, 6 h. [b] Identified as methyl octanoate by treating crude product solution with methanol–BF_3 reagent.

For the more active platinum catalysts, the principal side reactions are (a) the formation of small quantities of branched (α-methyl) acid esters, in this case methyl 2-methylheptanoate, and (b) isomerization of the 1-heptene to internal isomers, notably *cis*- and *trans*-2-heptene. Normally less than 10% of the 2-heptene is isomerized further to *cis*- and *trans*-3-heptene, and there is negligible *n*-heptane formation.

Effect of Olefin Structure. The sensitivity of the $(Ph_3P)_2PtCl_2$–$SnCl_2$ catalyst to substrate structure has been noted previously for both olefin hydrogenation[27] and hydroformylation;[22] here the preferred carbonylation catalyst, $(Ph_3As)_2PtCl_2$–$SnCl_2$, shows even greater sensitivity to the stereochemical requirements of the alkene (see Table III). Generally, monoalkenes are found to carbonylate readily only where the double bond is terminal. In the case of typical C_3–C_{20} linear 1-alkenes, the selectivity to desired linear carboxylic acid ester improves with increasing chain length (eq 6, mole selectivity in parenthesis), whereas the rate appears to reach a maximum around C_7.

$$C_3\ (76\%) < C_7\text{–}C_{14}\ (88\text{–}95\%) < C_{20}\ (95\%) \qquad (6)$$

The substitution of alkyl groups into the 1-alkene molecule acts to change both the activity and selectivity of the $(Ph_2As)_2PtCl_2$–$SnCl_2$. The observed pattern of behavior reflects primarily the steric effect of the alkyl substituent.[27] No carbonylation has been detected, for example, when the double bond is hindered by substituent groups on the α or β carbons (expt 31–33); this includes 2- and 5-decenes, cyclic olefins like cyclohexene, and β-substituted alkenes such as 2,4,4-trimethyl-1-pentene. On the other hand, where the substitution is one carbon removed from the double bond, as in the case of 3-methyl-1-pentene, carbonylation proceeds smoothly in high selectivity to give almost 100% methyl 4-methylhexanoate (expt 29). Even for δ-substituted materials, such as 4-methyl-1-pentene, selectivity for anti-Markownikoff addition remains close to 97 mol %.

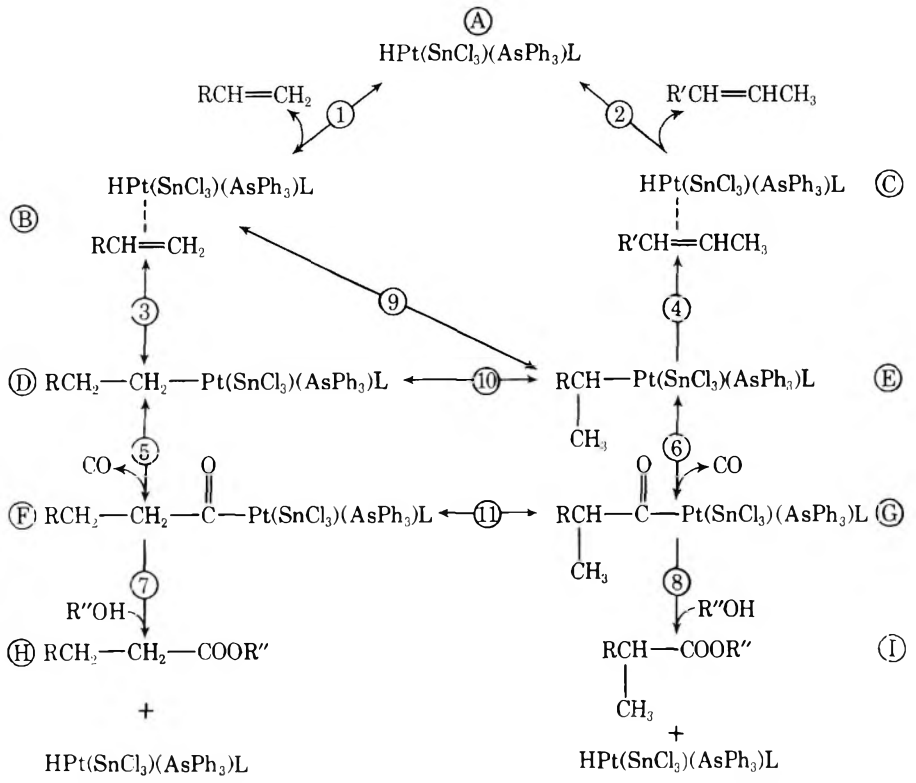
Effect of Nucleophile Structure. Carbonylation has been effected with a range of nucleophilic coreactants having mobile hydrogen atoms, including alcohols, water, mercaptans, and hydrogen halides. The trends parallel those for nickel and cobalt carbonyl catalysts.[2] Here the nucleophile structure has very little effect upon the catalyst selectivity, be it primary, secondary, or substituted alcohol, water, or thiol (Table IV), but the catalytic effectiveness varies by a factor of at least 20. Where oxygen is the attacking atom of the nucleophile, increased nucleophilicity[28] leads to improved yields of ester (eq 7). Competing addition reactions are prevalent with thiol (expt 35), but complexation with the platinum catalyst may account for the low conversion in this case. For methanol, at least, the rate of carbonylation is independent of the initial alkanol concentration provided that sufficient is present to satisfy the stoichiometry of eq 1.

$$ROH > HOH > PhOH \qquad (7)$$

Attempts to prepare fatty acid amides and anilides led to the formation of intractable tars. Carboxylic acid halogenides, such as octanoyl chloride, may be synthesized using HCl-treated solutions of the platinum salts in halogenated solvents such as methylene chloride.[29]

Temperature–Pressure Effects. While methyl octanoate synthesis may be carried out at temperatures of 25 °C or higher, and CO pressures up to 300 atm or more, a narrower range of conditions is necessary for preparative yields of ester with the $(Ph_3As)_2PtCl_2$–$SnCl_2$ catalyst.[14] The rate of carbonylation is slow below 60 °C and, as with related CO insertion reactions catalyzed by platinum,[30] ester preparations normally required pressures of about 70 atm.

Scheme I[a]



[a] Where L = $SnCl_3^-$, CO, chloride ion, or a solvent species.

No attempt has been made to correlate carbonylation activity with the nature of the solvent media,[2] but a range of moderately polar and nonpolar solvents has been found suitable for this synthesis. Methyl isobutyl ketone and dimethoxyethane were the standard solvents; *p*-dioxane, methylene chloride, and benzene also proved satisfactory.[14] *N,N*-Dimethylformamide inhibits carbonylation by forming stable adducts with the platinum complex.[31]

Discussion

The addition of tin(II) chloride to solutions of the complex $(Ph_3As)_2PtCl_2$ in non- or moderately polar solvents generates an active and very regiospecific carbonylation catalyst. This high regioselectivity is relatively insensitive to reaction parameters such as temperature, CO pressure, and solvent,[14] and the nature of the nucleophllic coreactant, but is significantly influenced by the structure of the alkene and the composition of the active catalysts. The observed trends, summarized in Tables I–IV, may be rationalized in terms of Scheme I, similar to that proposed for related catalysis.[4,32] Among stabilized Pt(II)–$SnCl_3$ catalysts the highest yields of linear carboxylic acid esters have been obtained with ligands of low basicity and high π-acceptor strength, such as $AsPh_3$, $AsClPh_2$, and $P(OPh)_3$ (eq 2 and 3). Likewise there appears to be a close parallel between catalyst activity and the π-acceptor strength of the MX_3^- cocatalyst (eq 4 and 5). For the preferred composition then, $(Ph_3As)_2PtCl_2$–$SnCl_2$, this combination of ligands, by lowering the electron density of the platinum, should favor both initial platinum hydride formation[20,21] and subsequent attack by nucleophiles such as CO and the multiple bonds of the olefin.[33]

With regard to the regioselectivity of the carbonylation, removal of electron density from the platinum metal center may also be expected to lower the hydridic character of the catalyst,[15] thereby favoring Markownikoff addition of Pt–H to the olefin (step 9) and branched acid ester formation via intermediates such as E and G. This increased acidity of the hydride is generally small,[15] however, and for $AsPh_3$ and $SnCl_3^-$ more than offset by the combined steric effects of these bulky ligands. Molecular models show that a combination of such ligands provides a particularly sterically hindered Pt complex, A, in which steric constraints should act to favor both anti-Markownikoff Pt–H addition (step 3) and high equilibrium concentrations of the less sterically hindered straight-chain σ-alkyl and σ-acyl Pt complexes such as D and F.

Similar reasoning based on the steric requirements of these highly crowded platinum catalysts may account for the observed selective carbonylation of only terminal olefins and the changes in product linearity with α-olefin structure (Table III), for example, the improvement in ester linearity from a low of 76 mol % for the least hindered homologue, propylene (expt 25), to near 100% for certain partially hindered α olefins such as 3-methyl-1-pentene (expt 29). Since internal, cyclic, and β-substituted α olefins are not carbonylated under these conditions, branched acid ester products likely originate not from 1-alkene isomerization and carbonylation of free internal isomer, but rather via Markownikoff Pt–*H* addition to the olefin (step 9) and/or isomerization of the σ-alkyl and σ-acyl intermediates to less favored forms (e.g., D → E and F → G). Preferential complexation of the platinum catalyst with 1-alkenes is consistent also with the observed selective carbonylation of internal–terminal olefin mixtures[34] (expt 34).

It may be noted that analogues of the hydridoplatinum species A and B have been prepared previously,[20,35] as have phosphine-stabilized platinum–alkyl complexes[36,37] and platinum–acyl species analogous to F, under more forcing conditions.[30] Intermediate platinum carbonyls such as $Pt(CO)(EtOH)(PPh_3)_2(SnCl_3)_2$ have also been isolated by the carbonylation of phosphine treated platinum–tin solutions.[38] However, while maximum catalyst activity is realized in this work at Sn:Pt mole ratios of about 10 (expt 14, 22–24), no Pt–Sn complexes with Group 5B ligands have been isolated having more than two $SnCl_3^-$ ions per plati-

num.[24] As in related catalysis,[33] it is likely that several interdependent equilibria exist prior to carbonylation, with at least partial displacement of the organoarsine ligand being consistent with (a) the relatively low sensitivity of the isomer distribution (selectivity 90–98 mol %) to significant changes in Group 5B ligand structure (Table I) and (b) the slower carbonylation rate in the presence of excess organoarsine (expt 4). Mixed complexes such as $(Ph_3As)_2PtCl(SnCl_3)$ are known,[39] although $SnCl_2$ may be readily displaced by other strong back-bonding ligands[24] such as CO.

Experimental Section

Materials. Carbon monoxide was CP grade. Reagents and solvents were commercial samples, and olefins were generally of high purity, and were freed of peroxides prior to use by passage through a column of neutral alumina. The platinum halide complexes, $PtCl_2(AsPh_3)_2$,[40] $PtCl_2(PPh_3)_2$,[40] $PtCl_2(SbPh_3)_2$,[40] $PtCl_2[P(OPh)_3]_2$,[21] $PtCl_2(SPh_2)_2$,[20] $PtCl_2$(o-phenanthroline),[41] and $Pt(CN)_2(PPh_3)_2$[21] were prepared by the published methods. Similar techniques were used to prepare $PtCl_2[PPh(CH_3)_2]_2$, $PtCl_2(Ph_2AsCH_2CH_2AsPh_2)$, $PtCl_2(AsPh_2Cl)_2$, and $PtI_2(AsPh_3)_2$. Hydrated tin(II) chloride, $SnCl_2 \cdot 2H_2O$, was used throughout as cocatalyst, except where specified.

General Procedures. The extent of carbonylation and the distribution of products were estimated by GLC. Olefin and ester analyses were both carried out with 4–10-ft columns of 10–20% polyphenyl ether (five rings, Analabs Inc. GP77) on 60/80 mesh Chromosorb G. High molecular weight fractions were also analyzed with the aid of a 4-ft column of 7% SE-30 on Chromosorb G. The esters were isolated by preparative GLC and by distillation, and identified by a combination of GLC, ir, NMR, mass spectrometric, and elemental analyses techniques.

After some preliminary experiments to establish suitable carbonylation conditions, most catalyst screening was carried out in a 600-ml glass-lined rocking autoclave under the conditions specified in Tables I and II. Rates of carbonylation were measured using a 300-ml capacity, glass-lined autoclave equipped with Magnadrive stirrer and sampling valve.

Synthesis of Methyl Octanoate. Dichlorobis(triphenylarsine)platinum(II) (0.5–20 mmol) and tin(II) chloride dihydrate (2.5–20 mmol) were added to a N_2-saturated mixture of methyl isobutyl ketone (75 ml), methanol (5–15 ml) and 1-heptene (50–200 mmol). The mixture was stirred for 2–5 min to dissolve the solid catalyst, and the loaded liner containing the deep red liquid charge was transferred to the autoclave. The autoclave was sealed, deoxygenated with a purge of N_2, and heated to 80 °C under 200 atm of carbon monoxide. After the reactor was rocked at this temperature for 3–6 h, the apparatus was allowed to cool, and the clear reddish-brown, liquid product recovered. Typical analyses data were as follows: 1-heptene conversion 95%, yield of methyl C_8 acid ester 92%, selectivity to linear methyl octanoate 93 mol %, material balance 97%.

The methyl C_8 acid ester may be recovered from the crude product liquid by fractional distillation in vacuo. Anal. Calcd for $C_7H_{15}COOCH_3$: C, 68.3; H, 11.4. Found: C, 68.4; H, 11.6.

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Registry No.—$((C_6H_5)_3As)_2PtCl_2$, 16242-55-0; (DIARS)$PtCl_2$, 14647-20-2; $[(C_6H_5O)_3P]_2PtCl_2$, 16337-54-5; $[(p\text{-}ClC_6H_4)_3P]_2PtCl_2$, 57606-46-9; $[(C_6H_5)_3P]_2PtCl_2$, 10199-34-5; $[(p\text{-}MeOC_6H_4)_3P]_2PtCl_2$, 57606-47-0; $[C_6H_5(CH_3)_2P]_2PtCl_2$, 30759-88-7; $[(C_6H_5)_3Sb]_2PtCl_2$, 16337-53-4; $[(C_6H_5)_2S]_2PtCl_2$, 50525-38-7; (1,10-PHEN)$PtCl_2$, 18432-95-6; $[(C_6H_5)_3P]_4Pt$, 14221-02-4; $[(C_6H_5)_2ClAs]_2PtCl_2$, 57606-48-1; $SnCl_2$, 7772-99-8; $As(C_6H_5)_3$, 603-32-7; $[(C_6H_5)_3As]_2PtI_2$, 24151-00-6; $[(C_6H_5)_3As]_2Pt(CN)_2$, 16242-57-2; SnI_2, 10294-70-9; $GeCl_2$, 10060-11-4; $PbCl_2$, 7758-95-4; $SbCl_3$, 10025-91-9; $SnCl_4$, 7646-78-8; methyl octanoate, 111-11-5; methyl isobutyl ketone, 108-10-1.

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Catalytic Activity in the Reversion of an Energy Storing Valence Photoisomerization

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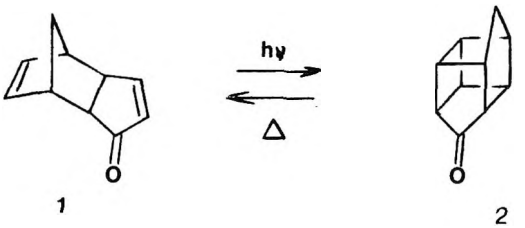
The quantum yield of valence photoisomerization of *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (1) to cage isomer 2 is 0.35–0.40 in several solvents. Upon irradiation at 330–380 nm the chemical yield of isomer 2 is essentially quantitative. Cage isomer 2 is thermally stable to 295 °C where slow decomposition occurs to give a mixture of products. Upon treatment with catalytic amounts of complexes of Rh(I) at 140–180 °C, 2 may be reverted to 1 in high yield. Catalysis kinetics are well behaved and first order in Rh(I) complex and substrate 2 during the initial stages of isomerization, after which the rate of reaction slows precipitously owing to catalyst instability. Initial isomerization rates establish relative catalytic activity: $Rh_2(CO)_4Cl_2$ > $Rh_2(NOR)_2Cl_2$ ~ $Rh(PPh_3)_3Cl$ (NOR = norbornadiene). The slow rate of catalyzed isomerization for 2 is striking in comparison with that for quadricyclenes, hexamethylprismane, cubanes, and homocubanes especially in view of the exothermicities for these reactions which are similarly large. A crude ordering of substrate activity (40 °C) obtains: quadricyclenes ~ prismane ~ cubanes > homocubanes > 2 (a 1,8,4,7-bishomocubane). The system 1 → 2 (ΔH = 16 kcal/mol) stores 8% of absorbed electronic excitation energy as chemical potential energy.

Although the capability to produce thermodynamically unstable molecules in organic photochemical reactions has been so widely exploited to be even taken for granted, a systematic quantitative assessment of the extent to which electronic excitation energy can be converted to chemical potential energy has not been made. Such a survey that might extend over many classes of photochemical reaction has direct relevance to possible photochemical conversion of solar energy and gains theoretical importance upon recognition of the intimacy of ground and excited state potential surfaces for highly endoergic photoreactions which are potentially thermally reversible. Important among criteria[1] for an efficient energy storage system employing an interconversion of isomers A and B are (1) system photochromism, i.e., a change in light absorption properties during photoreaction such that for certain wavelengths of excitation a photostationary state rich in B is assured; (2) a large positive ground state enthalpy A → B; (3) a quantum efficiency for A → B approaching unity; (4) a kinetic stability for B which matches the objective of energy storage (e.g., synthesis or energy conversion, normally significant stability for B somewhat above room temperature). We assess here the excitation energy storage capability of one system, 1 → 2, with focus on the mode of retrieval of latent heat in the thermal back reaction which is catalyzed by transition metal complexes and for which several important structure–reactivity relationships are apparent.

$$A \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} B$$

Results and Discussion

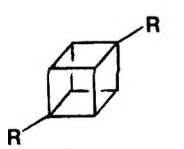
Dienone 1 was prepared and photolyzed as previously reported[2] and cage isomer 2 was obtained on a preparative scale as sole product in good yield. Irradiation of 1, which displays an n,π^* maximum at 340 nm, using a Rayonet chamber reactor and RUL 3500 lamps (330–380 nm), was followed as a function of time. Monitoring of absorbance of 1 and 2 revealed an isosbestic point at 310 nm, and GLC analysis of photolysis mixtures confirmed that the photoisomerization was remarkably clean. With 330–380 nm excitation the "photostationary"[3] mixture consisted of >99% isomer 2.[4] The material balance during irradiation of 1 vs. a GLC internal standard was >98%. Quantum yields for photoisomerization in several solvents (valerophenone actinometry[5]) are shown in Table I. The progress of photoisomerization at constant lamp intensity revealed that the yield is undiminished as a function of time to very high conversion for moderately concentrated samples.



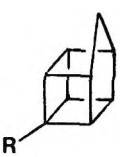
1 2

3, R = H
4, R = CO_2Me

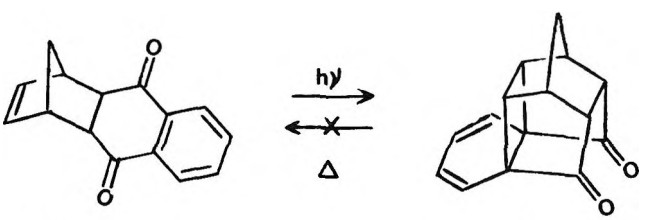
5



6, R = H
7, R = CO_2Me



8, R = H
9, R = CO_2Me



10 11

The assessment of energy storage capability follows with the simple calculation of "Q value", as suggested by Calvert[1a]

$$Q = \frac{(\phi)(\Delta F)(100)}{E(h\nu)_{av}}$$

Table I. Quantum Yields for Photoisomerization 1 → 2[a]

Solvent	Quantum yield[b]
Acetonitrile	0.37 ± 0.02
Benzene	0.38 ± 0.02
Diglyme	0.40 ± 0.02

[a] 0.07 M samples, 330–380 nm, 30 ± 1 °C. [b] Valerophenone actinometer (ϕ = 0.33, ref 5).

where ϕ, ΔF, and $E(h\nu)_{av}$ are quantum yield, the ground-state free-energy change (kcal/mol) for the photoreaction, and the average energy/photon absorbed (kcal/Einstein), respectively. We may confine our attention to the amount of energy stored only as latent, recoverable heat and replace ΔF with ΔH (2 → 1), or −16.4 kcal/mol determined by combustion calorimetry.[6] With ϕ = 0.4 and $E(h\nu)_{av}$ = 80 kcal/Einstein (350 nm), Q = 8%. Thus, storage of electronic excitation energy as chemical potential energy in the **1, 2** couple is appreciable (particularly in view of the relatively high excitation energy involved) and compares favorably with the capabilities noted for inorganic systems[1a] (Q generally <10%).

Sealed-tube pyrolysis of **2** in diphenyl ether (DPE) at 295° led to slow decomposition. The production of some tarry material was apparent, and NMR analysis showed that a mixture of products was obtained. This mixture was not identified but presumed to be akin to the products (including **1**) reported[7] for the flow pyrolysis of **2** at very high temperatures. The rate of decomposition of **2** was estimated ($k = 1 \times 10^{-4}$ sec^{-1}).

The thermal isomerization of 2 → 1 could be carried out more respectably in the presence of transition metal catalysts at moderately high temperatures. For example, 5 mol % of $Rh_2(CO)_4Cl_2$ affected virtually quantitative reversion to **1** in diglyme-d_{14} (DG) or diphenyl ether (DPE) at 140°. While NMR analysis indicated a >95% organic material balance, the separation of a gray-black metallic material (unidentified) during isomerization suggested catalyst instability. In a control experiment, $Rh_2(CO)_2Cl_2$ slowly deposited a gray-black substance on heating in solvents alone, at 140 °C. At high catalyst concentrations (~5 mol %) the rate of isomerization could be followed (NMR) over 2 half-lives and shown to be first order in substrate. At low catalyst concentrations (~0.5 mol %) first-order substrate disappearance plots were linear initially but deviated at about 1 half-life, with catalyzed isomerization finally coming to an end before completion. Under these circumstances the **1, 2** pair could not be "cycled" through sequential photolysis–pyrolysis steps. Attempts to bring about isomerization using $Pd(PhCN)_2Cl_2$, $AgClO_4$, Rh/C, Pd/C, K_2PtCl_4, $CuSO_4$, and *p*-toluenesulfonic acid under a variety of heterogeneous and homogeneous conditions at elevated temperatures were unsuccessful.

The catalysts which uniformly brought about isomerization 2 → 1 were the complexes of Rh(I). A ranking of these catalysts was attempted using initial disappearance rates for **2**. First-order plots were quite good at 10–40% conversion, giving rate constants which along with initial catalyst concentrations produced second-order rate constants as shown in Table II. (See paragraph at end of paper regarding supplementary material.) That a classical second-order catalytic rate law was obeyed is supported by experiments in which initial catalyst and substrate concentrations were varied. Thus, a plot of the first-order rate constants for disappearance of **2** vs. $[Rh_2(CO)_4Cl_2]$ (sevenfold range) was linear, and in experiments with $Rh_2(NOR)_2Cl_2$ (NOR = norbornadiene) a nearly threefold change in substrate concentration did not affect the calculated first- and second-order rate coefficients. Apparently the catalyst destruction

Table II. Kinetic Data[a] for the Catalyzed Isomerization 2 → 1

Substrate concn, M	Catalyst (concn, M)	Solvent	Temp, °C	k, M^{-1} sec^{-1}
1.7	$Rh_2(CO)_4Cl_2$ (0.02–0.14)	DG	140	1.0×10^{-2}[b]
1.3	$Rh_2(CO)_4Cl_2$ (0.005)	DG	160	7.1×10^{-2}
1.7	$Rh_2(CO)_4Cl_2$ (0.007)	DPE	180	1.0×10^{-1}
1.0–2.6	$Rh_2(NOR)_2Cl_2$ (0.061)	DG	180	1.8×10^{-3}
1.7	$Rh(PPh_3)_3Cl$ (0.07)	DPE	180	3.0×10^{-3}

[a] Obtained from pseudo-first-order rates at low conversion. Estimated rate constant error ± 20%. [b] Obtained graphically from plot of first-order rate constant for appearance of **1** vs. catalyst concentration.

which mitigated high conversion and cycling experiments was slow enough at the required temperatures (perhaps requiring an induction period) that the initial portion of the catalyzed isomerization was kinetically well behaved. Within the range of substrate concentration used, we did not observe Michaelis–Menten type kinetic behavior (denoting a rapid preequilibrium of substrate and catalyst) which has been documented in several transition metal catalyzed valence isomerization systems.[8]

The extreme reluctance of **2** to isomerize is somewhat surprising in view of the facile catalyzed ring openings of quadricyclenes (**3, 4**) to norbornadienes, hexamethylprismane (**5**) to hexamethyl(Dewar benzene), and cubanes (**6, 7**) and homocubane (**8**) to their tricyclic diene isomers.[9] In order to make a semiquantitative comparison of the organic substrates we have calculated relative rates for valence isomerization catalyzed by $Rh_2(NOR)_2Cl_2$ at 40 °C, a temperature for which rate data for **6–8** were available (Table III). For **2–5** the rates at 40 °C were obtained by extrapolation from data at other temperatures. Since activation parameters for these systems are not available, we have used for the extrapolation a frequency factor (log A = 7) similar to those reported for relevant valence isomerizations catalyzed by Rh(I) complexes.[14] Also included for reference in Table III are enthalpies of valence isomerization. Reasons for the markedly low reactivity of **2** in comparison with a family of caged substrates are not readily apparent. The presence of the carbonyl group in **2** might be responsible for a rate retardation of only about two orders of magnitude.[18] This deceleration has been noted previously for the quadricyclene (compare **3** and **4**)[14a] and cubane (compare **6** and **7**)[13] series and has been rationalized (with particular reference to the homocubane series, **8** vs. **9**) in terms of electronic and steric factors.[9d] Solvent effects are not likely a significant contributor to rate differences in view of the modest acceleration in more polar solvent noted for catalyzed isomerization of **4**.[11]

Early theories concerning transition metal catalyzed valence isomerization[19] suggest a role for ring strain release in determining rate. However, the measured or calculated negative enthalpies of isomerization for **2–6** are similarly large. Comparison among ring types reveals the relative reactivity order, quadricyclenes ~ prismane ~ cubanes > homocubanes > **2** (a 1,8,4,7-bishomocubane) (compare **3, 5, 6** with **8** and in the carbonyl-substituted series **4, 7** with **9** and **2**). Although *overall* molecular strain appears not to be a rate-determining factor, the degree and kind of *local* bond deformation must influence the reactivity order. Thus, as models show that the bond angle requirements become less severe in the series cubanes > homocubane > bishomocubane (the cyclobutane rings begin to pucker in-

Table III. Comparative Kinetics and Heat of Reaction Data for Valence Isomerization of Cage Compounds Catalyzed by $Rh_2(NOR)_2Cl_2$

Cage substrate	k_{obsd}, M^{-1} sec^{-1} (temp, °C)	Solvent	Ref	k_{rel} (40 °C)[a]	ΔH, kcal/mol
2	1.8×10^{-3} (180)	DG	This work	1	−16.0[c]
3	5.5×10^{-2} (−26)	$CDCl_3$	10	1×10^8	−21.2[d]
4	2.8×10^{-2} (60)	$CDCl_3$	11	3×10^5	−18.5[d]
5	9.7×10^{-3} (−30)[b]	$CHCl_3$	12	3×10^7	−31.7[e]
6	14 (40)	$CDCl_3$	13	4×10^8	−16.7[f]
7	1.1×10^{-1} (40)	$CDCl_3$	13	3×10^6	
8	1.4×10^{-2} (40)	C_6H_6	9a	4×10^5	

[a] Except for 6–8 calculated from absolute values extrapolated to 40 °C, using the Arrhenius equation and log A = 7. [b] Calculated from the reported half-life. [c] From heats of combustion, ref 6. [d] From DSC measurements, ref 15. [e] From DSC measurements, ref 16. [f] From MINDO/3 calculations of heats of formation, ref 17.

creasingly), so do the relative rates of rhodium-catalyzed decomposition vary, with a rate retardation of ~10^3 for each replacement of a zero-carbon bridge with a one-carbon bridge. This dependence on the degree of local bond angle deformation (and on the number of deformed bonds) is no doubt related to the ability of the strained ring to act as a base,[9e,20] an oxidizing agent,[13,21] a nucleophile,[28] or as an electron donor,[20] types of interaction of strained σ bonds with metals which have been considered. We wish to emphasize that the remarkable reactivity of caged saturated substrates with metals may be confined to a rather small group of compounds.[23] High energy content is insufficient ground for reactivity while an effect related to the enforcement of bond angles in the cage structure is largely rate determining.

We have examined the reversibility of one other system capable of storing electronic excitation energy. For the photochromic isomerization of **10**[25] (350 nm), one can estimate an impressively large energy storage efficiency (Q = 25%) from the reported quantum yield (ϕ = 1)[25] and an estimate[26] of the heat of reaction **17** → **16** (ΔH ~ −20 kcal/mol). Dione **11** is thermally stable to 150° and resists catalytic reversion to **10** at elevated temperatures in the presence of $Rh_2(CO)_4Cl_2$, $Rh(PPh_3)_3Cl$, $Pd(PhCN)_2Cl_2$, or *p*-toluenesulfonic acid despite a large potential exothermicity. The reverse valence isomerization is no doubt mitigated by those same inductive and steric substituent effects and bond angle deformation effects already discussed for **2** and other cage substrates.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded with a Joelco C-60-HL spectrometer. Gas chromatography was performed on a Varian Aerograph 1400 instrument (FI detector) equipped with a disc integrating recorder.

Thiophene-free benzene was washed with sulfuric acid until no further coloration of the acid layer appeared, then with aqueous $NaHCO_3$ solution and distilled water, and finally distilled over phosphorus pentoxide. Valerophenone (Aldrich) and diglyme were distilled under reduced pressure. Acetonitrile (spectroquality, Matheson Coleman and Bell), dodecane (spectrophotometric grade, Aldrich), diglyme-d_{14} (DG) (Merck), $Rh_2(CO)_4Cl_2$ (Alfa), and anhydrous and hydrated rhodium trichloride (Alfa) were used without further purification.

$Pd(PhCN)_2Cl_2$,[27] $Rh_2(NOR)_2Cl_2$,[28] and $Rh(PPh_3)_3Cl$[29] and tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (**1**)[30] were prepared according to literature procedures. The 1,4-naphthoquinone–cyclopentadiene adduct **16** was prepared and photolyzed to give **17** as previously described.[25]

Preparative Irradiation of Dienone 1.[2] A nitrogen-purged solution of **1** (1.0 g, 6.8 mmol) in 330 ml of acetonitrile was irradiated with a 450-W Hanovia medium pressure lamp (Pyrex filter). Over 250 min of irradiation, an isosbestic point at 305 nm and a "photostationary" [3] state (some 10% of **1** remaining) developed (uv analysis). Removal of solvent in vacuo gave a viscous oil which was crystallized from light petroleum. The waxy solid was sublimed (~2 mm) to give 750 mg of **2** (75%), mp 118–121 °C (lit. mp 124–126 °C), λ_{max} 295 nm (ϵ 22).

Quantum Yield Determinations. Solutions containing known concentrations of dienone **1** and dodecane (internal standard for GLC analysis) were prepared for irradiation in 15-mm Pyrex tubes. The solutions were deoxygenated by bubbling nitrogen for 30 min through long syringe needles inserted through rubber serum caps. The Rayonet RS photochemical reactor was fitted with four RUL 3500 lamps. The temperature in the reaction chamber was maintained at 30 ± 1 °C by means of a fan which circulated air from the bottom of the chamber. A Merry-Go-Round unit (Southern New England Ultraviolet) provided a sample tube mounting for parallel irradiation.

The conversion of valerophenone to acetophenone[5] (ϕ = 0.33) in irradiations in parallel with **1** was monitored for actinometric purposes. Small differences in absorbance for actinometer and **1** over the lamp emission range (330–380 nm) were calculated using solution percent transmittance values and lamp relative intensity (data from the supplier) at intervals of 2–5 nm. GLC analysis (8 ft × 0.125 in. 3% FFAP on 80–100 Chromosorb W column at 90–150 °C) of actinometer and sample product (vs. dodecane) provided relative conversion values which were corrected for differential detector response.

Catalyzed Pyrolysis of 2. Solutions of **2**, catalyst, solvent, and diphenylmethane (NMR internal standard) were prepared in heavy-wall NMR tubes (Wilmad) which had been washed with acid, base, distilled water, and acetone and dried. The sample tubes were evacuated through several freeze–thaw cycles and sealed. Pyrolyses were carried out in an oil bath insulated and thermoregulated (±0.5 °C) using an I^2R Therm-o-watch as described previously.[31] Pyrolysis tubes were totally immersed in the well-stirred baths and examined periodically after quenching in ice water.

NMR analysis for the appearance of **1** (vinyl protons) vs. diphenylmethane (methylene protons) provided conversion data (generally 10–40%) from which rate constants could be calculated using the integrated first-order rate equation. Second-order rate constants derived from these values and catalyst concentrations. (See supplementary material.)

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Supplementary Material Available. Tables of rate data for catalyzed isomerization of **2** (3 pages). Ordering information is given on any current masthead page.

Registry No.—**1**, 5530-96-1; **2**, 15584-52-8.

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Conformational Control by Carbinyl Hydrogens. Implications and Applications

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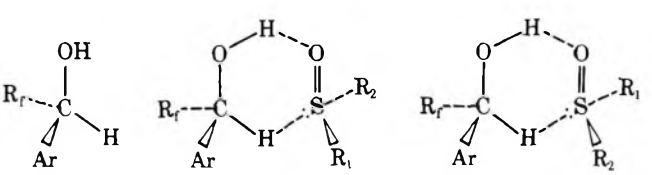
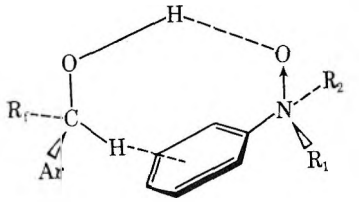
"Acylation shifts" and Eu(fod)$_3$ gradients of the carbinyl hydrogens of a variety of esterlike derivatives of secondary alcohols are substantially enhanced when the carbinyl carbon bears a trifluoromethyl group. This enhancement is not steric in origin and is attributed to weak intramolecular bonding between the carbinyl hydrogen and the carbonyl oxygen which populates conformations placing the carbinyl hydrogen near to and approximately in the plane of the magnetically anisotropic carbonyl. Here, this hydrogen may be deshielded (acylation shift) or shifted downfield (gradient) upon coordination of the carbonyl oxygen to Eu(fod)$_3$. The concept of conformational control by carbinyl hydrogen bonding can be used to account for prior instances of chemical behavior such as chromatographic properties, NMR chemical shifts, and asymmetric induction.

Prior papers dealing with chiral NMR solvents have explained the ability of these solvating agents to cause the spectra of enantiotopic solutes to become nonequivalent as a consequence of the formation of transient diastereomeric solvates.[1-6] Further, it has been proposed that these solvates assume conformations which place enantiomeric solute nuclei in different orientations with respect to a magnetically anisotropic substituent of the chiral solvating agent. Accurate knowledge of the conformational behavior of these diastereomeric solvates would enable one to directly relate the observed spectral differences to the stereochemical differences of the solvates.[7] For chiral solvents of known absolute configuration, this type of spectral interpretation would amount to *simultaneous determination of the absolute configuration and enantiomeric purity of the solute*. Clearly, an understanding of the factors underlying the conformational behavior of the transient diastereomeric solvates is essential to the successful employment of this technique.

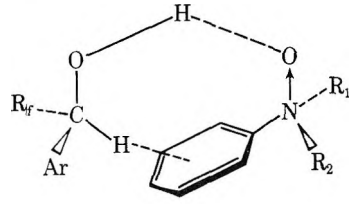
Specific solvation models have been advanced[1,2] to account for the NMR nonequivalence shown by enantiomeric sulfoxides or enantiomeric tertiary amine oxides in the presence of chiral type 1 alcohols. After initial intermolecular hydrogen bonding, a weaker but intramolecular bonding between the carbinyl hydrogen of 1 and a second basic site in the solute is postulated to afford chelatelike conformations exemplified by **2a,b** and **3a,b**. Such conformations would place enantiomeric solute nuclei (R_1 or R_2) in different orientations with respect to the aromatic substituent of chiral alcohol 1. Hence, the resultant average chemical shift



1 2a 2b



3a



3b

differences between solute enantiomers stem from differential shielding effects in the diastereomeric solvates and are easily relatable to solute stereochemistry.

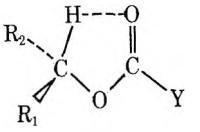
While the ability of the hydroxyl of a type 1 alcohol to hydrogen bond to basic solutes is easily demonstrated, the ability of the carbinyl hydrogen of 1 to exert a secondary bonding interaction on weakly basic sites such as π electrons or unshared electron pairs is less obvious. The question of the existence of this latter type of bonding is a rather important one, for the conformational control proposed to result thereby does account for the occurrence of enantiomeric spectral nonequivalence and does correctly correlate the senses of this nonequivalence with the absolute configurations of a wide variety of solute classes, these models not being restricted solely to sulfoxides or amine oxides.[12] Inasmuch as the determination of absolute configuration is a frequently encountered problem, the development of a convenient, reliable, easily understood method for simultaneously determining absolute configuration and enantiomeric purity would be quite useful. For this reason, we have investigated several systems where such weak intramolecular bondings might result in demonstrable conformational control, an observation which would have considerable bearing upon the merits of the proposed solvation models.

In the case of esterlike derivatives of type 1 alcohols, weak intramolecular bonding between the carbinyl hydrogen and the carbonyl oxygen would be quite analogous to the previously postulated chelating interactions and should exert some degree of conformational control.

There are two reasons to anticipate this conformational control. First, the case for *intermolecular* hydrogen bonding between chloroform and several bases has been reviewed by Pimentel and McClelland and judged to be sound.[13] Equally relevant, evidence for the *intermolecular* hydrogen bonding of chloroform to the π cloud of benzene has been offered.[14] Secondly, the $T\Delta S$ term for *intramolecular* hydrogen bonding is essentially zero, whereas it has been estimated to be ca. 3 kcal/mol for *intermolecular* hydrogen bonding in solution.[15] Thus, a weak bonding interaction of a given enthalpy will be rather more effective in controlling conformation populations in the *intramolecular* case than in controlling extent of association in the *intermolecular* case.

In a sense, the carbinyl hydrogen of 1 is analogous to the methine hydrogen of chloroform in that both have three inductively electron-withdrawing groups in the α position. To the extent that the "acidity" of the carbinyl hydrogen plays a role in the postulated CHB, the presence or absence of the electronegative trifluoromethyl group should have predictable consequences in terms of the extent of conformational control arising through CHB.

Several years ago, the acylation shift undergone by carbinyl hydrogen resonances upon acylation of alcohols was related by Culvenor[16] to the population of conformers similar to 4 which place the carbinyl hydrogen in or near the



4

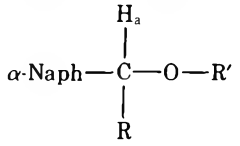
plane of the magnetically anisotropic acyl carbonyl group. Culvenor offers no forthright explanation as to the reasons underlying the population of conformer 4, although it was known at that time from microwave data that the methoxyls of methyl formate and methyl acetate are cis to carbonyl oxygen but ca. 25° out of the carbonyl plane.[17] X-ray data for several crystalline esters also indicates close approach (2.22 Å) of the carbinyl hydrogen to carbonyl oxygen in the solid state.[18] Conformations approximating 4 have been used by Karger[19] and Helmchen[10] to account for the elution order of diastereomeric esters and amides upon gas and thin layer chromatography. Almost invariably, the reasons for the population of conformers like 4 are assumed to be steric or else not mentioned at all. An exception to this is Mathieson, who contemplated, on the basis of his x-ray work, the possible existence of a weak intramolecular bonding force between the carbinyl hydrogen and carbonyl oxygen of an ester.[18] However, Mathieson concluded that "repulsive forces" are dominant in determining ester conformation although "subsidiary local forces" play a role as well. If real, CHB could play a substantial role in populating conformations like 4.

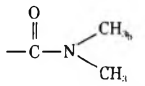
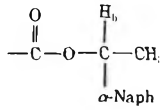
Results and Discussion

On steric grounds, the conformational behavior of 1,1,1-trifluoro-2-propyl acetate (6) is expected to be intermediate between that of 2-propyl acetate (7) and 3,3-dimethyl-2-butyl acetate (8), since the van der Waals diameter of the trifluoromethyl group (5.1 Å) is intermediate between that of methyl (4.0 Å) and *tert*-butyl (6.2 Å). If steric effects alone are responsible for population of conformations like 4, then the acetylation shifts are expected to occur in the order 7 < 6 < 8. However, if the presence of the trifluoromethyl group in 6 results in increased population of conformations like 4, a greater acetylation shift would be observed for the fluoro alcohol than for the other two alcohols.[20] In actuality, the acetylation shift of 1,1,1-trifluoro-2-propanol is 1.48 ppm vs. 1.25 ppm for 2-propanol and 1.20 ppm for 3,3-dimethyl-2-butanol. Similar arguments apply to the *N,N*-dimethyl carbamates of these three alcohols, but, again, the fluoro alcohol undergoes the greater (1.10 vs. 0.80 and 1.06 ppm) "acylation shift".

Further studies were conducted on 2,2,2-trifluoro-1-(1-naphthyl)ethanol[22] (10) (of interest as a chiral NMR additive for determining absolute configurations and enantiomeric purities[1]) and its nonfluorinated analogues, 1-(1-naphthyl)ethanol (11) and 2,2-dimethyl-1-(1-naphthyl)-propanol (12). Conversion of these alcohols respectively into acetates, **13a–c**, *N,N*-dimethyl carbamates, **14a–c**, chloroformates, **15a,b**, or carbonate **16**[23] results in a greater "acylation shift" for fluoro alcohol **10** than for alcohols **11** or **12** (see Table I). This result is consistent with the view that trifluoromethyl group more heavily populates conformations which place the carbinyl hydrogen near the deshielding carbonyl oxygen. It is obvious that these greater acylation shifts do not stem solely from steric origins, since trifluoromethyl is intermediate in size between methyl and *tert*-butyl. Only in the case of the sulfinates **17a,b**,[23] derived from reaction of **10** and **11** with 2-propylsulfinyl chlo-

Table I. Carbinyl Hydrogen "Acylation Shifts" and Eu(fod)$_3$ Gradients of Some Alcohol Derivatives



Compd	R′	R	Acylation shift H_a, ppm[a]	Eu(fod)$_3$ H_a, ppm	Gradient[b] H_b, ppm
13a–c		CF_3	1.33	9.4	6.4
		CH_3	1.15	5.9	7.4
		$C(CH_3)_3$	1.15	6.7	7.0
14a–c		CF_3	1.30	17.	8.7
		CH_3	1.05	11.	12.
		$C(CH_3)_3$	1.05	13.	10.
15a,b		CF_3	1.28		
		CH_3	1.00		
16		CF_3	1.20 (H_a) 1.05 (H_b)	2.6	0.8
17a,b		CF_3	0.58	19.	
		CH_3	0.55	10.	

[a] Chemical shifts were obtained for quite dilute carbon tetrachloride solutions at 28 °C. [b] 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 0.99 to 0.97.

ride, are the acylation shifts similar. By the preceding criteria, one might conclude that there is no significant difference in the conformational behavior of these sulfinates. Data to be subsequently presented make this seem unlikely, and it is tentatively concluded that the asymmetric magnetic anisotropy about the sulfinyl group coincidentally occasions the similar "acylation" shifts. A relevant observation here is that the preferred conformation of thiacyclohexane 1-oxides places the sulfinyl oxygen in an axial position.[24,25] It has been suggested[24,25] and supported[26] by calculations that there is an attractive interaction between the axial oxygen and the axial γ hydrogens amounting to 0.37 kcal/mol, even though the γ hydrogens would not be expected to be especially acidic.

Lanthanide Shift Studies. Independent supportive evidence for the ability of an α-trifluoromethyl group to preferentially populate type **4** conformations comes from a study of the effect of Eu(fod)$_3$ upon the chemical shifts of the carbinyl hydrogens of the aforementioned derivatives of alcohols **10**, **11**, and **12**. Eu(fod)$_3$ is known to coordinate to the carbonyl oxygen in a variety of carbonyl containing compounds. While thus coordinated, it exerts a deshielding influence on nearby protons which diminishes with increasing distance from the lanthanide. The effect of Eu(fod)$_3$ concentration upon the chemical shifts of the carbinyl hydrogen and acetyl methyl resonances of dilute carbon tetrachloride solutions of acetates **13a–c** was determined. At low ratios of Eu(fod)$_3$/substrate, these plots are essentially straight lines, the least-squares slopes of which are given in Table I. If one uses the slope (gradient) of the acetyl methyls as an index of the extent of coordination by the Eu(fod)$_3$, one infers that acetates **13b,c** coordinate more strongly than fluorinated acetate **13a**. This is expected a priori since the electron-withdrawing trifluoromethyl should reduce the basicity of the carbonyl oxygen of **13a** relative to **13b,c**. Nevertheless, the gradient for the carbinyl hydrogen of fluoroacetate **13a** is greater than those of **13b** or **13c** even before allowance is made for **13a**'s reduced degree of coordination. Competition experiments between equal concentrations of **13a** and **13b** show that Eu(fod)$_3$ coordinates preferentially to **13b** by a factor of ca. 7:1. Judging from the acetyl methyl gradients, the more hindered **13c** is complexed to a slightly lesser degree than **13b**. However, from the carbinyl hydrogen gradients, the additional steric bulk appears to favor conformations placing the carbinyl hydrogen near the lanthanide while complexed.

Other data in Table I show that the rates at which the carbinyl hydrogens are shifted downfield by Eu(fod)$_3$ addition varies from derivative to derivative as changes in the basicities of the carbonyl oxygens influence the extent of coordination to Eu(fod)$_3$. For example, the carbonate **16** appears to coordinate more weakly than any of the carbamates. Note however, that within a class, the carbinyl hydrogen of the derivative of fluoro alcohol **10** is shifted more strongly than that derived from **11** or **12** *despite the fact that the carbonyl basicities of the derivatives of* **10** *must be less than those of* **11** *or* **12**. As further illustration of this point, note that the *N*-methyl group cis to the carbonyl oxygen in *N,N*-dimethyl carbamate **14a** (derived from fluoro alcohol **10**) is not shifted downfield as strongly as those in carbamates **14b** and **14c**, derived from **11** and **12**. A competition experiment employing equal concentrations of **14a** and **14b** shows that Eu(fod)$_3$ preferentially coordinates to **14b** by a 3:1 margin. Use of the mixed carbonate **16** avoids problems of differing extents of coordination to Eu(fod)$_3$ since both types of carbinyl hydrogens are present in the same molecule. Again, it is the carbinyl hydrogen derived from **10** which is most strongly influenced by the addition of Eu(fod)$_3$, the initial slope of its $\Delta\delta$ vs. Eu(fod)$_3$ curve being over twice that of its less acidic partner. Finally, despite probable basicity differences, the greater Eu(fod)$_3$ gradient of the carbinyl hydrogen of fluoro alcohol **10** is especially evident for sulfinates **17a** and **17b** which, it may be recalled, show no difference in their "acylation" shifts.

The preceding results clearly indicate that the carbinyl

hydrogens of the derivatives of fluoro alcohol **10** are, on the average, closer to the complexed Eu(fod)$_3$ than their counterparts in the derivatives of **11** and **12**. Again, this is most readily explained in terms of a weak bonding between the carbinyl hydrogen and the carbonyl oxygen. The strength of this interaction would appear to increase with increased "acidity" of the carbinyl hydrogen. Presumably, the carbonyl (or sulfinyl) oxygen retains some basic character during coordination to Eu(fod)$_3$ and still serves as an acceptor for CHB.[27] While one must not be unmindful of the ability of shift reagents to influence conformational equilibria,[28] it seems reasonable that CHB in the uncoordinated derivative would be even stronger.

The preceding data clearly demonstrate that the α-trifluoromethyl group plays a substantial role in preferentially populating type **4** conformations of esterlike derivatives of type **1** alcohols. This demonstration is of considerable importance, since it furnishes analogy for the conformations, **2a,b, 3a,b,** invoked to account for the ability of chiral type **1** alcohols to promote ^{1}H NMR spectral nonequivalence for enantiomeric sulfoxides and amine oxides. This analogy does not hinge upon the correctness of the rationale (i.e., CHB) for the reason underlying the population of these conformations, although this too is important in that real understanding of the origin of the conformational preference might suggest structural modifications which would further bias this conformational preference.

The results of Karger et al.[29] on the correlation of stereochemistry with gas chromatographic elution order of diastereomeric esters of secondary alcohols can be rationalized on the basis of preferred conformations in which the carbinyl hydrogen is in or near the plane of the carbonyl group. Similar conformations have been used by Helmchen et al.[10] in correlating stereochemistry with chromatographic and NMR behavior of some diastereomeric amides and by Moser et al.[8,9] in correlating stereochemistry and ^{1}H NMR spectral differences between diastereomeric esters of secondary alcohols.

It is suggested that carbinyl hydrogen bonding may play an active role in causing the population of the aforementioned conformers and may also manifest itself during some asymmetric induction reactions.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. Proton NMR spectra were obtained with Varian Associates A-60A, A56-60, or HA-100 instruments. Infrared spectra were obtained with a Beckman IR-12. Mass spectra were determined using a Varian MAT CH-5 spectrometer. Microanalyses were performed by J. Nemeth and his colleagues.

Acetates. All of the acetates used in this study were prepared using the following procedure. Acetyl chloride (0.517 g, 6.63 mmol) was added via syringe to a cold (−78°C) solution of racemic alcohol (ca. 4.5 mmol) and triethylamine (0.67 g, 6.6 mmol) in 30 ml of fluorotrichloromethane. After 15 min, the amine hydrochloride was removed, the solvent evaporated, and the crude acetate molecularly distilled. In some instances, the acetates were purified by chromatography on silica gel with methylene chloride using a system similar to that described.[30]

1-(1-Naphthyl)-2,2,2-trifluoroethyl acetate (13a) was an oil (95% yield): NMR (CCl_4) δ 2.13 (s, C–CH_3), 6.95 (quartet, CH), 7.30–8.15 ppm (multiplet, $C_{10}H_7$); ir (neat) 3090, 2970, 1760 (C=O), 1370, 1270, 1215, 1135, 1065 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 268 (69.05, M$^+$), 225 (4.5), 209 (12.5), 157 (100).

1-(1-Naphthyl)ethyl acetate (13b) was an oil (>95% yield): NMR (CCl_4) δ 1.6 (d, C–CH_3), 1.97 (s, C–CH_3), 6.55 (quartet, CH), 7.15–8.10 ppm (multiplet, $C_{10}H_7$); ir (neat) 3090, 3000, 1745 (C=O), 1450, 1360, 1250, 1175, 1110 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 214 (61.99, M$^+$), 172 (37.38), 155 (91.86), 154 (99), 128 (34).

1-(1-Naphthyl)-2,2-dimethylpropyl acetate (13c) was a yellow oil (85% yield): NMR (CCl_4) δ 0.96 [singlet, C(CH_3)$_3$], 2.00 [singlet, C(=O)CH_3], 6.45 (singlet, CH), 7.30–8.20 ppm (multiplet, $C_{10}H_7$); ir (neat) 3060, 2990, 1750, 1640, 1550, 1370, 1350, 1120 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 256 (11.70, M$^+$), 199 (22.53), 157 (100), 129 (21.86), 127 (7.80).

Carbamates. All of the carbamates used in this study were made by the following procedure. Sodium hydride–mineral oil dispersion (5.0 mmol) was added to the alcohol (ca. 4.5 mmol) in 10 ml of dry tetrahydrofuran. When gas evolution ceased, *N,N*-dimethylcarbamoyl chloride (0.60 g, 5.6 mmol) was added in small portions. After 15 min, 100 ml of water was added and the solution was extracted twice with 25-ml portions of methylene chloride. The dried extracts were concentrated and the residual material chromatographed on silica gel with methylene chloride using a system similar to that described.[30]

1-(1-Naphthyl)-2,2,2-trifluoroethyl-*N,N*-dimethyl carbamate (14a) was straw-colored crystals (90% yield): mp 65.6–66.2; NMR (CCl_4) δ 2.91 (broad s, NCH_3), 6.94 (quartet, CH), 7.32–8.14 ppm (multiplet, $C_{10}H_7$); ir (KBr) 3000, 2070, 1740 (C=O), 1410, 1578, 1190, 1100 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 297 (35.7, M$^+$), 209 (100), 159 (26.5), 121 (100).

Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 60.89; H, 4.73; N, 4.73. Found: C, 61.35; H, 4.74; N, 4.80.

1-(1-Naphthyl)ethyl-*N,N*-dimethyl carbamate (14b) was an oil (>90% yield): NMR (CCl_4) δ 1.69 (d, C–CH_3), 2.90 (s, NCH_3), 6.45 (quartet, CH), 7.3–8.1 ppm (multiplet, $C_{10}H_7$); ir (neat) 3050, 2970, 2900, 1705 (C=O), 1600, 1380 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 243 (95.09, M$^+$), 155 (100).

1-(1-Naphthyl)-2,2-dimethylpropyl-*N,N*-dimethyl carbamate (14c) was an oil (65% yield): NMR (CCl_4) δ 1.00 [singlet, C(CH_3)$_3$], 2.92 (broad singlet, NCH_3), 6.39 (singlet, CH), 7.3–8.2 ppm (multiplet, $C_{10}H_7$); ir (neat) 3050, 2990, 1710, 1625, 1390, 1370, 1190 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 285 (9.47, M$^+$), 228 (16.8), 127 (3.09), 72 (100).

Chloroformates. Chloroformates were prepared in a manner analogous to that used by Altner.[31]

1-(1-Naphthyl)-2,2,2-trifluoroethyl chloroformate (15a) was purified by gel permeation chromatography on Bio-Beads SX-12 with CH_2Cl_2, and was obtained as a yellow liquid (71% yield): NMR (CCl_4) δ 6.90 (quartet, CH), 7.2–8.1 ppm (multiplet, $C_{10}H_7$); ir (neat) 3075, 1775 (C=O), 1540, 1358, 1260, 1240, 1190, 1140 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 288 (76, M$^+$), 219 (26), 209 (100), 188 (35), 182 (45).

Anal. Calcd for $C_{13}H_8ClF_3O_2$: C, 54.30; H, 2.78; Cl, 12.15. Found: C, 54.36; H, 2.79; Cl, 12.20.

1-(1-Naphthyl)ethyl chloroformate (15b) was purified by gel permeation chromatography on Bio-Beads SX-12 with CH_2Cl_2, and was obtained as a yellow liquid (60% yield): NMR (CCl_4) δ 2.0 (d, C–CH_3), 6.40 (quartet, CH), 7.2–8.2 ppm (multiplet, $C_{10}H_7$); ir (neat) 3050, 2980, 1730 (C=O), 1510, 1445, 1380, 1275, 1220 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 192 (73), 191 (37), 190 (100, M − CO_2), 174 (35), 157 (24), 156 (100), 155 (100), 150 (78), 138 (46), 126 (99), 115 (67), 86 (11).

1-(1-Naphthyl)-2,2,2-trifluoroethyl 1′-(1′-Naphthyl)ethyl Carbonate (16). 1-(1-Naphthyl)-2,2,2-trifluoroethyl chloroformate (**15a**, 2 g, 6.95 mmol) and racemic 1-(1-naphthyl)ethanol (**11**, 1.19 g, 6.95 mmol) were dissolved in 50 ml of benzene. After addition of pyridine (0.549 g, 6.95 mmol), the reaction mixture was refluxed for 48 h. This mixture was then filtered and the filtrate was concentrated and chromatographed on a Bio-Bead SX-12 gel permeation column. The effluent was monitored at 280 nm. The first major fraction to be eluted was carbonate **15** (yield 40%): NMR (CCl_4) δ 1.98 (d, C–CH_3), 6.45 (quartet, CH_3C**H**), 6.82 (quartet, CF_3C**H**), 7.1–8.1 ppm (multiplet, $C_{20}H_{14}$); ir (neat) 3090, 3000, 1745 (C=O), 1450, 1400, 1380, 1270, 1250, 1140 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 424 (57.78, M$^+$), 173 (94.45), 172 (100), 129 (100), 128 (54).

Sulfinates. The sulfinate esters described in this paper were prepared following a procedure developed by Hoekstra.[32]

1-(1-Naphthyl)-2,2,2-trifluoroethyl 2-Propyl Sulfinate (17a). Racemic fluorocarbinol **10** (0.994 g, 4.39 mmol) and pyridine (0.372 ml, 0.365 g, 4.61 mmol) were dissolved in 6 ml of $CFCl_3$ in a serum-stopped flask and cooled to −78 °C. 2-Propylsulfinyl chloride (5.0 mmol) was then added via syringe and the reaction mixture was shaken for 15 min. The reaction mixture was chromatographed on silica gel with CH_2Cl_2. Recrystallization of the high R_f diastereomer from 1:1 CH_2Cl_2–hexane afforded colorless crystals: mp 61.5–64.5 °C; NMR (CCl_4) δ 1.22 (d, C–CH_3), 2.76 (septet, CH), 6.19 (quartet, CH), 7.25–8.15 ppm (multiplet, $C_{10}H_7$); ir (KBr) 3060, 2995, 1635, 1515, 1470, 1400, 1345, 1240, 1120 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 316 (3.22, M$^+$), 209 (100), 127 (12.33).

Anal. Calcd for $C_{15}H_{15}F_3O_2S$: C, 57.09; H, 4.70. Found: C, 57.10; H, 4.65.

Although the high R_f diastereomer was used for NMR studies, its carbinyl hydrogen has essentially the same chemical shift as that of the low R_f diastereomer: NMR (CCl_4) δ 1.19 (d, C–CH_3), 2.72 (septet, CH), 6.14 (quartet, CH), 7.25–8.15 ppm (multiplet, $C_{10}H_7$).

1-(1-Naphthyl)ethyl 2-Propyl Sulfinate (17b). An oily mixture of diastereomers was obtained, inseparable by chromatography on silica gel (>90% yield): NMR (CCl_4) δ 1.15 [d, $C(CH_3)_2$], 1.75 (d, C–CH_3), 2.58 (septet, CH), 5.92 (quartet, CH), 7.22–8.15 ppm (multiplet, $C_{10}H_7$); ir (neat) 3070, 2970, 1540, 1235, 1135, 1070 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 262 (14.87, M^+), 155 (96.74), 154 (100), 128 (100).

Acknowledgment. This work has been supported in part by grants from the National Institutes of Health (Grant GM 14518) and from the National Science Foundation (Grant MPS 74-21812).

Registry No.—**10,** 17556-44-4; **11,** 57605-95-5; **12,** 57573-88-3; **13a,** 57573-89-4; **13b,** 57573-90-7; **13c,** 57573-91-8; **14a,** 57573-92-9; **14b,** 57573-93-0; **14c,** 57573-94-1; **15a,** 57573-95-2; **15b,** 57573-96-3; **16,** 57573-97-4; **17a** diastereomer a, 57573-98-5; **17a** diastereomer b, 57573-99-6; **17b** diastereomer a, 57574-00-2; **17b** diastereomer b, 57574-01-3; acetyl chloride, 75-36-5; *N,N*-dimethylcarbamoyl chloride, 79-44-7.

References and Notes

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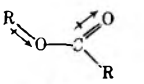

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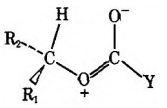
Bothner-By to explain why the methyl of propionaldehyde prefers to be cis to the carbonyl oxygen.[21] On the other hand, the electronegativity of the trifluoromethyl group will cause the ground-state basicities of both the alkoxyl and carbonyl oxygens of acetate **6** to be less than those of acetates **7** and **8**. Hence, the latter will be better able to support resonance as depicted in **9** and better able to serve as an intramolecular hydrogen bond acceptor. Moreover, the electronegativity of the trifluoromethyl group should also tend to diminish the magnitudes of the bond dipoles shown in **5** and hence possibly reduce the population of the cis conformer. On the basis of the latter three effects only, the acetylation shift of the fluoro alcohol would be expected to be *less* than that of the two other alcohols.



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(27) Coordination to $Eu(fod)_3$ will make the carbonyl oxygen a poorer receptor for CHB and some loss of CHB presumably results. This loss could conceivably be greater for the less acidic carbinyl hydrogens than for the more acidic carbinyl hydrogens and hence explain the substantially larger gradients of the latter.
(28) Since coordination to lanthanide makes the region about the carbonyl (sulfinyl) oxygen sterically more congested, one could conceivably preferentially populate the rotamer which places the smallest carbinyl substituent (i.e., the hydrogen) toward the lanthanide. Two aspects of this hypothesis worth contemplating are (a) the entire alkoxyl substituent could simply rotate away from lanthanide if steric interactions were too severe; (b) the carbinyl hydrogen gradients do not simply parallel the bulk of the alkyl substituent. The consequences of electronic interactions between the trifluoromethyl and the lanthanide shift reagent occurring in concert with steric forces cannot yet be predicted.
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Dehalogenation and Condensation Reactions of Molybdenum Carbonyls with Activated Halides

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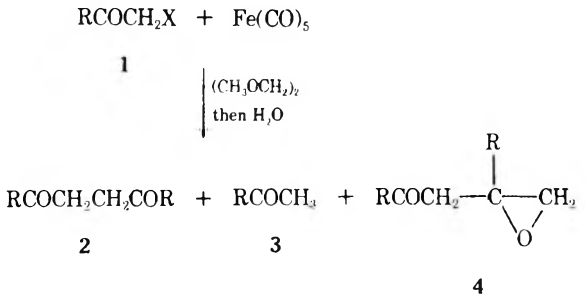
Molybdenum hexacarbonyl reacts with α-halo ketones in 1,2-dimethoxyethane to form monoketones and α,β-unsaturated carbonyls in generally good combined yields. Triphenylphosphine molybdenum pentacarbonyl and tetrabutylammonium pentacarbonyl molybdenate(0) are also useful reagents, but chromium and tungsten hexacarboxyls exhibit low reactivity toward α-halo ketones. Coupling products were obtained by treatment of dichlorodiphenylmethane or 9-bromofluorene with $Mo(CO)_6$.

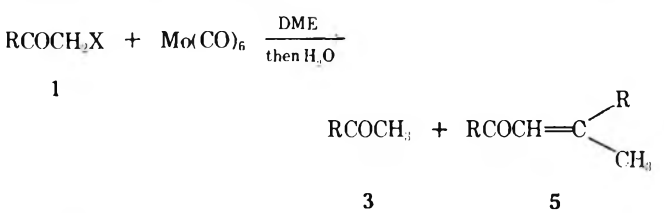
Reaction of iron pentacarbonyl with α-halo ketones (**1**) affords 1,4-diketones (**2**), monoketones (**3**), and, in several instances, β-epoxy ketones (**4**). 1,4-Diketones were usually



the major products of these reactions. Evidence has been presented for initial oxidative addition of the trigonal bipyramidal $Fe(CO)_5$ by the α-halo ketone to give an octahedral intermediate.[1] It was of considerable interest to learn the effect of metal carbonyl configuration on the reaction course. Oxidative addition to octahedral group 6 metal carbonyls such as molybdenum hexacarbonyl [$Mo(CO)_6$] is a much less common process than for $Fe(CO)_5$, since formation of a neutral seven-coordinate intermediate would be required for $Mo(CO)_6$. Rather, treatment of certain halides with $Mo(CO)_6$ under stoichiometric or catalytic conditions results in the generation of radical (from CCl_4, CBr_4, $CCl_3COOC_2H_5$)[2] or ionic (from RCOCl)[3] intermediates. We now wish to report that α-halo ketones react in a different, and interesting, manner with group 6 metal carbonyls as compared to $Fe(CO)_5$.

Results and Discussion

Monoketones (**3**) and α,β-unsaturated ketones (**5**) were obtained by treatment of α-halo ketones with an equimolar amount of $Mo(CO)_6$ in refluxing 1,2-dimethoxyethane (DME, 48 hr) and then with water. The yields, melting

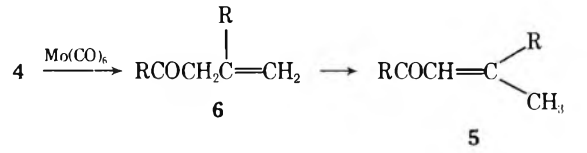


points of new compounds, and pertinent spectral data for the reaction products are given in Table I.

The α-halo ketone–$Mo(CO)_6$ reaction afforded the methyl ketone as the major or only product, except for **1**, R = p-$NO_2C_6H_4^-$, which gave the chalcone **5**, R = p-$NO_2C_6H_4$, as the major product. The other group 6 metal carbonyls, chromium hexacarbonyl and tungsten hexacarbonyl, were much less reactive than $Mo(CO)_6$ giving low conversions even after reaction times of 6 days with 2-chloro-2′,3′,4′,5′,6′-pentamethylacetophenone. However, treatment of the latter with triphenylphosphine molybdenum pentacarbonyl resulted in the formation of pentamethylacetophenone in 76% yield.

There are several important differences in the behavior of iron and molybdenum carbonyls toward α-halo ketones: (1) monoketones (**3**), usually the major products formed using $Mo(CO)_6$, were generally obtained as minor products with $Fe(CO)_5$; (2) coupling to 1,4-diketones is the major reaction pathway for $Fe(CO)_5$, while $Mo(CO)_6$ affords α,β-unsaturated carbonyls and no 1,4-diketones; (3) the $Mo(CO)_6$–**1** reaction can be effected in the presence of a nitro group, while such a functionality undergoes reduction on treatment with $Fe(CO)_5$;[4] (4) substitution of a carbon monoxide ligand by triphenylphosphine in the reactant $Mo(CO)_6$ results in increased product yields, while α-halo ketones were inert to triphenylphosphine iron tetracarbonyl.[1]

The different reactivity patterns, products, and product distributions for the iron and molybdenum carbonyl–α-halo ketone reactions suggest that these reactions are likely occurring via different pathways. However, the mechanistic details, for the group 6 metal carbonyl reactions, are not clear. It seemed conceivable that the α,β-unsaturated ketones (**5**) could arise by deoxygenation of a β-epoxy ketone (**4**) to the β,γ-unsaturated ketone **6**, followed by isomerization to **5**. The major reaction pathway, however, for epoxide–$Mo(CO)_6$ reactions is rearrangement rather than deoxygenation.[5] Conversion of an α-halo ketone such as **1**, R = p-$C_6H_5C_6H_4^-$, to **3** and **5** was also observed using tetrabutylammonium bromopentacarbonyl molybdenate [$(C_4H_9)_4N^+Mo(C)_5Br^-$]. The latter did not effect aldol condensation of **3** to **5**.[8]



Molybdenum hexacarbonyl did effect coupling of several other types of activated halides. Tetraphenylethylene (**8**) was formed in 65% yield by treatment of dichlorodiphenylmethane (**7**) with $Mo(CO)_6$. No chlorodiphenylmethane, diphenylmethane, or 1,2-dichloro-1,1,2,2-tetraphenylethane was isolated in this reaction. Tetraphenylethylene was also obtained by treatment of 1,2-dichloro-1,1,2,2-tetraphenylethane with $Mo(CO)_6$. Iron pentacarbonyl also reacts with **7** or with 1,2-dichloro-1,1,2,2-tetraphenylethane to give tetraphenylethylene.[1]

Treatment of 9-bromofluorene (**9**) with $Mo(CO)_6$ gave bisfluorenyl (**10**) in 40% yield, but no fluorene. The lack of

Table I. Products Obtained from Reaction of Group 6 Metal Carbonyls with α-Halo Ketones in DME[a]

α-Halo ketone (1)	Registry no.	Metal carbonyl	Registry no.	Products[b]	Registry no.	New compd mp,[c] °C	Yield, %	Ir, ν_{CO},[d] cm^{-1}	NMR (CH_3),[e] δ, p.p.m.	MS, M+ m/e
2-Bromo-4′-phenylacetophenone	135-73-9	$Mo(CO)_6$	13939-06-5	3, R = p-$C_6H_5C_6H_4$	92-91-1		51	1685	2.60	196
				5, R = p-$C_6H_5C_6H_4$	57196-64-2	196–197	16	1650	2.56	374
2-Chloro-2′,3′,4′,5′,6′-pentamethylacetophenone	57196-63-1	$Mo(CO)_6$		3, R = 2,3,4,5,6-$(CH_3)_5C_6$	2040-01-9		51	1680	2.44	190
				5, R = 2,3,4,5,6-$(CH_3)_5C_6$	57196-65-3	177–178	<1	1662		362
		$W(CO)_6$	14040-11-0	3, R = 2,3,4,5,6-$(CH_3)_5C_6$			12[f]			
		$Cr(CO)_6$	13007-92-6	None						
		$(C_6H_5)_3PMo(CO)_5$	14971-42-7	3, R = 2,3,4,5,6-$(CH_3)_5C_6$			76			
2,4′-Dibromoacetophenone	99-73-0	$Mo(CO)_6$		3, R = p-$BrC_6H_4^-$	99-90-1		25	1683	2.58	
				5, R = p-$BrC_6H_4^-$	7509-25-3		14	1655	2.54	380
2-Bromo-4′-methoxyacetophenone	2632-13-5	$Mo(CO)_6$		3, R = p-$CH_3OC_6H_4^-$	100-06-1		46	1678	2.54	150
				5, R = p-$CH_3OC_6H_4^-$	16197-83-4		18	1652	2.51	282
2-Bromo-4′-nitroacetophenone	99-81-0	$Mo(CO)_6$		3, R = p-$NO_2C_6H_4^-$	100-19-6		20	1682	2.67	165
				5, R = p-$NO_2C_6H_4^-$	7509-21-9		26	1660	2.70	312
1-Adamantyl bromomethyl ketone	5122-82-7	$Mo(CO)_6$		3, R = 1-adamantyl	1660-04-4		14	1712	2.07	
				5, R = 1-adamantyl	57196-66-4	185–186	6	1680	1.97	338

[a] 1:1 ratio of $Mo(CO)_6$:1. Reaction time of 48 hr. [b] Satisfactory (±0.4%) analytical (C, H) data were obtained for new compounds. [c] The melting point or boiling point and spectral data for known products were in good agreement with literature data. [d] Chloroform as solvent. [e] $CDCl_3$–Me_4Si as internal standard. [f] Reaction time of 6 days. after 48 hr reaction, 3, R = 2,3,4,5,6=$(CH_3)_5C_6$, was formed in 2% yield.

$$Ph_2CCl_2 \xrightarrow[DME]{Mo(CO)_6} Ph_2C{=}CPh_2$$

7 8

9 10

formation of fluorene indicates that **9** (and **7**) are generating different intermediates than those produced in α-halo ketone–$Mo(CO)_6$ reactions. For **9** and **7**, halogen atom transfer may be occurring to form a radical, which then undergoes coupling.[2]

Experimental Section

General. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were carried out by Drs. F. and E. Pascher, Bonn, West Germany, and by Galbraith Laboratories Inc., Knoxville, Tenn. Infrared spectra were obtained on a Beckman IR20A spectrometer. NMR spectra were obtained on a Varian T-60 spectrometer, with tetramethylsilane used as the internal standard. Mass spectra were recorded on a Varian MS902 spectrometer.

We are grateful to the Climax Molybdenum Co. for providing generous quantities of molybdenum hexacarbonyl. This metal carbonyl was sublimed prior to use. Tungsten and chromium hexacarbonyls were purchased from Pressure Chemical Co. and used as received. Mr. C. C. Huang supplied us with a sample of triphenylphosphine molybdenum pentacarbonyl.[3] The organic reactants were commercial products and were recrystallized or distilled prior to use. Solvents were dried and purified by standard techniques. All reactions were run under an atmosphere of dry nitrogen.

Reaction of $Mo(CO)_6$ with α-Halo Ketones. A mixture of the α-halo ketone (8–10 mmol) and an equimolar amount of $Mo(CO)_6$, in dry DME (40–70 ml), was heated with stirring at 85–90° (oil bath temperature) for 48 hr. The solution was cooled and filtered (inorganic material) into 200–350 ml of ice water. The resulting precipitate was filtered and dried. Work-up was effected for the particular reactions as follows (see Table I for yields and pertinent physical data for the products).

A. 1 (R = p-$C_6H_5C_6H_4$). Continuous extraction (Soxhlet) of the solid with petroleum ether (bp 30–60°) afforded the methyl ketone **3**, R = p-$C_6H_5C_6H_4$. The α,β-unsaturated ketone **5**, R = p-$C_6H_5C_6H_4$, was isolated by treatment of the Soxhlet residue with chloroform, filtration, and evaporation of the filtrate.

B. 1 (R = 2′,3′,4′,5′,6′-$(CH_3)_5C_6$). Compound **3**, R = 2,3,4,5,6-$(CH_3)_5C_6$, was obtained by continuous extraction of the precipitate with petroleum ether. Extraction of the residue in the thimble with ether or ether–chloroform gave a trace amount of **5**, R = 2,3,4,5,6-$(CH_3)_5C_6$.

C. 1 (R = p-$BrC_6H_4^-$). Continuous extraction of the solid with petroleum ether gave **3**, R = p-$BrC_6H_4^-$. The nonextractable material was then continuously extracted with chloroform to give **5**, R = p-BrC_6H_4. Pure **5** was obtained by recrystallization from petroleum ether–benzene.

D. 1 (R = p-$CH_3OC_6H_4^-$). Extraction of the aqueous filtrate (no precipitate formed here) with ether gave an oil which was chromatographed on Florisil. Elution with benzene–petroleum ether gave **3**, R = p-$CH_3OC_6H_4$. Elution with benzene or benzene–chloroform (4:1) afforded pure **5**, R = p-$CH_3OC_6H_4$.

E. 1 (R = p-$NO_2C_6H_4^-$). The milky aqueous filtrate was extracted with ether, dried (Na_2SO_4), and evaporated to give a yellow semisolid. p-Nitroacetophenone (**3**, R = p-$NO_2C_6H_4$) was obtained by treating the semisolid mixture with 100 ml of petroleum ether–benzene (1:1) and decanting the solution, which was then evaporated in vacuo. Crystallization of the petroleum ether–benzene insoluble oil from hexane afforded **5**, R = p-$NO_2C_6H_4$.

F. 1 (R = 1-Adamantyl). The solid was dissolved in petroleum ether and chromatographed on Florisil. Elution with petroleum ether–benzene (2:1) gave **3**, R = 1-adamantyl. Elution with benzene afforded the unsaturated carbonyl **5**, R = 1-adamantyl.

Reaction of 2-Chloro-2′,3′,4′,5′,6′-pentamethylacetophenone with $W(CO)_6$. A mixture of **1**, R = pentamethylphenyl (1.80 g,

8.00 mmol), and $W(CO)_6$ (2.81 g, 8.00 mmol) in DME (40 ml) was heated to 90° for 48 hr. Work-up as described for the reaction of the same α-chloro ketone with $Mo(CO)_6$ gave **3**, R = pentamethylphenyl, in 2% yield, along with recovered starting materials. Using a reaction time of 6 days resulted in the formation of methyl ketone in 12% yield.

Reaction of 2-Chloro-2′,3′,4′,5′,6′-pentamethylacetophenone with Triphenylphosphine Molybdenum Pentacarbonyl. A DME (60 ml) solution of $(C_6H_5)_3PMo(CO)_5$ (2.611 g, 5.20 mmol) and α-chloro ketone (1.17 g, 5.20 mmol) was heated at 85–90° for 46 hr. The solution was cooled and filtered into ice–water. The resulting precipitate was filtered and dried. Continuous extraction of the solid with petroleum ether gave reasonably pure methyl ketone [$(C_6H_5)_3PMo(CO)_5$ as impurity] which could be furthur purified by column chromatography on Florisil using petroleum ether as eluent. No α,β-unsaturated carbonyl was obtained by treatment of the nonextractable material with ether–chloroform.

Reaction of 2-Bromo-4′-phenylacetophenone with Tetrabutylammonium Pentacarbonyl Molybdenate(0). A mixture of tetrabutylammonium pentacarbonyl molybdenate(0)[6] (0.918 g, 2.10 mmol) and 2-bromo-4′-phenylacetophenone (0.578 g, 2.10 mmol) in DME (45 ml) was heated at 90° for 48 hr. The reaction mixture was worked up as described in procedure A to give **3** and **5**, R = p-$C_6H_5C_6H_4$.

Reaction of Dichlorodiphenylmethane (7) with $Mo(CO)_6$. A mixture of dichlorodiphenylmethane (1.90 g, 8.00 mmol) and $Mo(CO)_6$ (4.20 g, 16.0 mmol) in dry DME (40 ml) was heated at 85–90° for 48 hr. The solution was cooled and poured into cold water. The resulting solid was filtered to give crude tetraphenylethylene (**8**). Chromatography of the latter on silica gel, using benzene as eluent, gave 0.864 g (65%) of pure **8**: mp 223.5–225.0° (lit.[1] mp 226–227°); mass spectrum m/e 332 (M^+).

Reaction of 1,2-Dichloro-1,1,2,2-tetraphenylethane with $Mo(CO)_6$. A mixture of 1,2-dichloro-1,1,2,2-tetraphenylethane (2.02 g, 5.00 mmol) and $Mo(CO)_6$ (2.37 g, 9.00 mmol) in DME (40 ml) was heated at 85–90° for 42. hr. Work-up as described for **7** gave tetraphenylethylene in 81% yield.

Reaction of 9-Bromofluorene with $Mo(CO)_6$. A solution of 9-bromofluorene (2.14 g, 8.60 mmol) and $Mo(CO)_6$ (2.29 g, 8.65 mmol) in DME (30 ml) was heated at 90–95° for 45 hr. The solution was cooled and filtered (inorganic) into ice water to give a white solid which was subsequently filtered. Recrystallization from benzene–ethanol gave 0.580 g (40%) of bisfluorenyl (**10**), mp 246–248° (lit.[7] mp 246°). Spectral data for **10** were in accord with data for authentic material.

Acknowledgments. We are grateful to the National Research Council of Canada for support of this work. We are indebted to Messrs. Jake Blair and Raj Capoor for mass spectral and NMR spectral determinations, respectively.

Registry No.—**7**, 2051-90-3; **8**, 632-51-9; **9**, 1940-57-4; tetrabutylammonium bromopentacarbonyl molybdenate, 32592-48-6; 1,2-dichloro-1,1,2,2-tetraphenylethane, 1600-30-2.

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(8) **Note Added in Proof.** Methylmanganese pentacarbonyl has recently been shown to induce aldol condensation of benzyl methyl ketone [R. L. Bennett and M. I. Bruce, *Aust. J. Chem.*, **28**, 1141 (1975)].

Kinetics of the Reaction of *n*-Butyllithium with 4-Methylmercaptoacetophenone in Benzene[1]

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Kinetics of the reaction of 4-methylmercaptoacetophenone (**2**) with excess n-butyllithium in benzene at 25.0 °C have been studied by ir and uv stopped-flow spectrophotometric techniques. The observed first-order rate constant increases rapidly as the concentration of n-butyllithium is increased from 0.014 to ca. 0.1 M, but the rate is not greatly enhanced by further increases in the concentration of alkyllithium. The rate of the reaction is increased by the presence of alkoxides in the alkyllithium reagent; addition of 0.001 M of the product alcohol to 0.1 M n-butyllithium increases the measured first-order rate constant by a factor of about 2. Some mechanistic implications of these observations are outlined.

The reaction of the ketone 2,4-dimethyl-4′-methylmercaptobenzophenone (**1**) with methyllithium in diethyl ether has been shown[2] to be first order in ketone and one-fourth order in methyllithium. These data are consistent with a mechanism for addition proceeding through monomer in equilibrium with tetrameric methyllithium. Other examples of reactions occurring through monomeric organolithium, which is in equilibrium with higher aggregates in ethereal solvents, include the addition of n-butyllithium[3] and phenyllithium[3] to benzonitrile, the addition of methyllithium to transition metal carbonyls,[4] the initiation of vinyl polymerization,[5,6] and the metalation of triphenylmethane.[7] The addition of alkyllithium reagents to styrene[8–10] and to 1,1-diphenylethylene[11,12] in aromatic solvents is also believed to proceed through monomeric species; however, for the addition of n-butyllithium to butadiene[13] and ethyllithium to 1,1-diphenylethylene[14] in aromatic solvents, monomer may not be the sole reactive species. In aliphatic solvents, alkyllithium reagent aggregates species appear to react with isoprene[15–17] and ethylene.[18]

The addition of lithium halides to diethyl ether solutions of methyllithium has been shown[2] to retard the rate of addition to ketone **1**. This is the expected result because the incorporation of lithium halides into methyllithium aggregates lowers the fraction of the organolithium present in monomeric form.[2]

In contrast to the rate-depressing effect of lithium halides in diethyl ether on the addition to ketones, alkoxides have been reported to either increase or decrease the reactivity of alkyllithium reagents in hydrocarbons. For example, the initiation of styrene polymerization in aromatic solvents,[19–21] the propagation of olefin polymerizations,[15,16,19,21,22] and the alkylation of naphthalene[23] are depressed by lithium alkoxides, while in contrast alkoxides

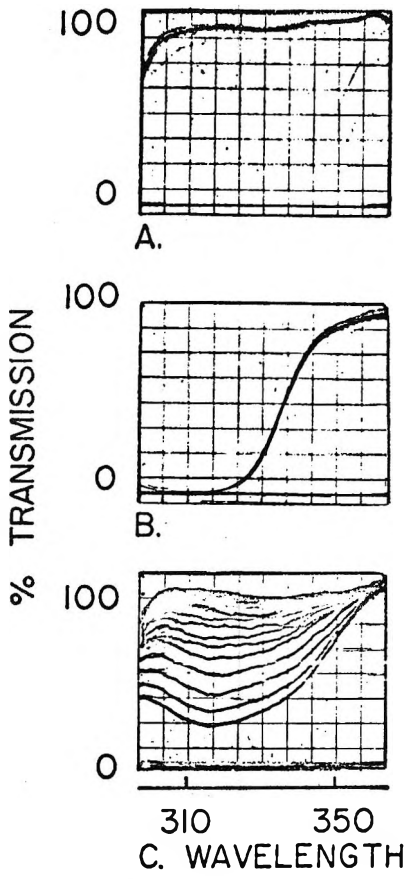
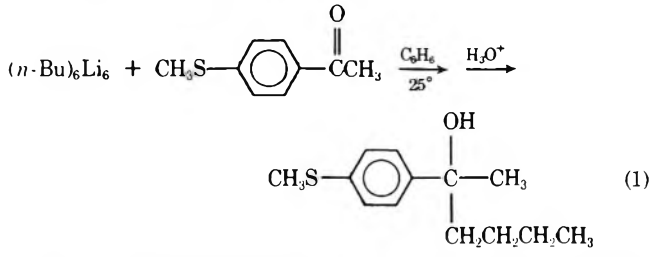


Figure 1. Transmission spectra of the reaction of 8×10^{-3} M *n*-butyllithium with 6.1×10^{-5} M 2,4-dimethyl-4′-methylmercaptobenzophenone in benzene at 25.0 °C: A, transmission spectrum of 8×10^{-3} M *n*-butyllithium in benzene; B, transmission spectrum of 6.1×10^{-5} M 2,4-dimethyl-4′-methylmercaptobenzophenone in benzene; C, transmission spectrum of the reaction mixture of 8×10^{-3} M *n*-butyllithium and 6.1×10^{-5} M 2,4-dimethyl-4′-methylmercaptobenzophenone in benzene at 25.0 °C, recorded 18.2 times per second. The first recorded line is the continuous flow spectrum, recorded at 0.03 s after mixing.

accelerated the rate of the initiation of olefin polymerization in aliphatic solvents,[15-17] the addition of ethyllithium[14] and *n*-butyllithium[24] to 1,1-diphenylethylene in benzene, the pyrolysis of *sec*-butyllithium[25] in octane and *tert*-butyllithium[26] in decalin, and the cleavage of *n*-butyl and *tert*-butyl ethers by *n*-butyllithium in heptane.[27,28]

In the present study, the kinetics of the reaction of *n*-butyllithium with 4-methylmercaptoacetophenone (**2**) in benzene are examined, eq 1. Reacting solutions were ob-



(1)

served by ir and uv stopped flow spectrophotometric techniques. The effect of added alkoxides is also considered.

Results and Discussion

The continuous flow uv spectrum of the reaction mixture of *n*-butyllithium and 4-methylmercaptoacetophenone (**2**) in benzene at 25.0 °C, recorded ca. 1 ms after mixing, indicates that the π–π^* absorption of ketone **1** is broadened, compared to the spectrum of ketone in the absence of *n*-butyllithium, and the apparent λ_{max} is shifted toward longer wavelengths. However, the ir spectrum of reacting solutions could not be distinguished from the spectrum of ketone **2** in the carbonyl stretching region. Only the band at 1690 cm^{-1} was observed. The use of the more hindered ketone, 2,4-dimethyl-4′-methylmercaptobenzophenone (**1**), makes it possible to record several spectra during the course of the reaction. This is illustrated in Figure 1 for the reaction of 8×10^{-3} M *n*-butyllithium with 6.1×10^{-5} M ketone **1** in benzene at 25 °C. The rapid scan uv spectrum of this reaction, recorded 18.2 times per second (**1**), indicated that the absorbance remained broad as it disappeared.

The presence of enhanced absorbance at longer wavelengths in the uv spectrum noted here is similar to the development of a resolved new absorbance in both the uv and ir in the reaction of ketones with methylmagnesium bromide.[29] In the case of the Grignard reagent, the long-wavelength uv absorbance was attributed to a complex between the organomagnesium reagent and the carbonyl oxygen which was subsequently converted to product.[29]

The kinetics of the reaction of 4-methylmercaptoacetophenone with *n*-butyllithium in benzene were studied by stopped-flow spectroscopy. A typical run, recorded at 330 nm, is illustrated in Figure 2. The integrated first-order rate constant calculated from Figure 2 is summarized in Table I. The reaction is first order in ketone under these concentration conditions, as shown in Figure 2 and Table I. The observed first-order rate constant for the reaction 0.125 M *n*-butyllithium with 5.6×10^{-4} to 1.8×10^{-2} M 4-methylmercaptoacetophenone in benzene at 25.0° was appropriately independent of the ketone concentration provided ketone was at least 10^{-3} M. A competing reaction, probably caused by alkoxides in the *n*-butyllithium reagent, caused k_{obsd} to be dependent on ketone concentration when ketone was less than 10^{-3} M (Table II).

Figure 3 is a plot of the observed first-order rate constant, k_{obsd} (Table III), vs. *n*-butyllithium concentration, measured under the conditions of excess lithium reagent. This plot shows that the reaction is not first order in alkyllithium because the rate of the reaction increases rapidly as the concentration of *n*-butyllithium is increased from 0.014

Table I. Reaction of 0.13 M *n*-Butyllithium with 1.3×10^{-3} M 4-Methylmercaptoacetophenone in Benzene at 25.0° C

Time, s	Absorbance at 330 nm	k_{obsd}, s^{-1} (integrated)
0.0	0.917	
0.01	0.602	42
0.02	0.394	42
0.03	0.255	43
0.04	0.159	44
0.05	0.093	46
0.06	0.056	47
0.07	0.040	45
0.08	0.022	47
	Least-squares rate constant	46.7

Table II. Effect of Ketone Concentration on the Observed First-Order Rate Constant for the Reaction of 0.19 M *n*-Butyllithium with 4-Methylmercaptoacetophenone (1) in Benzene at 25.0°C

10^3 ketone 1, M	k_{obsd}, s^{-1}
0.125	115
0.25	91
0.56	61
1.0	51
1.8	46
9.5	44
10.2	50

Table III. Summary of Observed Pseudo-First-Order Rate Constants for the Reaction of *n*-Butyllithium with 4-Methylmercaptoacetophenone in Benzene at 25.0°C

10 *n*-butyllithium, M	10^3 ketone, M	k_{obsd}, s^{-1}
0.14	1.50	30
0.19	1.60	33
0.21	1.45	34
0.26	1.45	34
0.27	1.45	33
0.29	2.26	37
0.32	1.60	31
0.37	1.50	32
0.41	2.26	39
0.47	1.60	34
0.50	1.50	34
0.64	1.60	37
0.65	2.28	36
0.67	1.60	34
0.85	2.28	40
0.92	1.6	40
1.5	2.28	46
2.6	1.32	42
3.8	1.32	44
4.0	1.32	44
6.3	1.32	48
7.0	1.32	50
7.7	1.22	50
8.8	1.22	49

to ca. 0.1 M, but the rate is not greatly enhanced by further increases in lithium reagent concentration.

These data are consistent with either of the idealized cases of reaction predominantly through a less associated species than the hexamer, eq 2–4, as we found earlier for methyllithium in diethyl ether[2a] or by a mechanism involving a ketone lithium reagent complex as was found in the analogous reactions of Grignard reagents, eq 5–7[29] The

$$\frac{1}{6}(n\text{-BuLi})_6 \overset{K_2}{\rightleftharpoons} n\text{-BuLi} \quad (2)$$

$$n\text{-BuLi} + \text{ketone} \xrightarrow{k_2} \text{product} \quad (3)$$

$$k_{obsd} = k_2K_2(n\text{-BuLi})_6^{1/6} \quad (4)$$

$$(n\text{-BuLi})_6 + \text{ketone} \overset{K_1}{\rightleftharpoons} \text{complex} \quad (5)$$

$$\text{complex} \xrightarrow{k_1} \text{product} \quad (6)$$

$$k_{obsd} = \frac{k_1K_1(n\text{-BuLi})_6}{1 + k_1(n\text{-BuLi})_6} \quad (7)$$

present data do not, of course, unambiguously distinguish between other fractional orders in butyllithium. However, the hexameric character of the butyllithium and the known one-fourth in the reaction of tetrameric methyllithium makes the one-sixth order a reasonable choice. The perturbation of the uv spectrum in the presence of *n*-butyllithium is consistent with the presence of complex; however, a quantitative assessment of its importance has not yet been possible because of considerable uncertainty in initial absorbance data which is attributed to variable amounts of alkoxide in different preparations of *n*-butyllithium. Other roles for a complex between *n*-butyllithium and the ketone in benzene suggested by the uv spectrum than the simple case outlined in eq 5–7 can be proposed. Furthermore, it should be noted that these equations suggest just one of many possible types of complex and pathway to product.

Trace amounts of lithium alkoxides were found to increase the rate of reaction of 4-methylmercaptoacetophenone with *n*-butyllithium (Table IV). For example, the addition of 0.001 M of the product alcohol to 0.1 M butyllithium increases the measured first-order rate constant by a factor of about 2. However, if the alkoxide is generated by addition of alcohol to the ketone so that alkoxide is formed upon rapid mixing with the lithium reagent in the stopped flow apparatus, the reaction is found to be independent of alkoxide concentration (Table V). Alkoxide is, of course, also generated during the course of the reaction by the addition of the lithium reagent to the carbonyl group. However, even with 0.01 M ketone, the reaction was not autocatalytic within the accuracy of the measurements.

The failure of alkoxide generated during the reaction to have the same accelerating effect as that of alkoxide added to the lithium reagent prior to the addition of the ketone suggests that the rate of addition to the carbonyl group of ketone is fast relative to the equilibration of the lithium alkoxide with *n*-butyllithium which produces the species responsible for the enhanced reactivity. This is consistent with available data on intermolecular exchange of ethyllithium in toluene,[30–32] which shows an exchange time of ca.

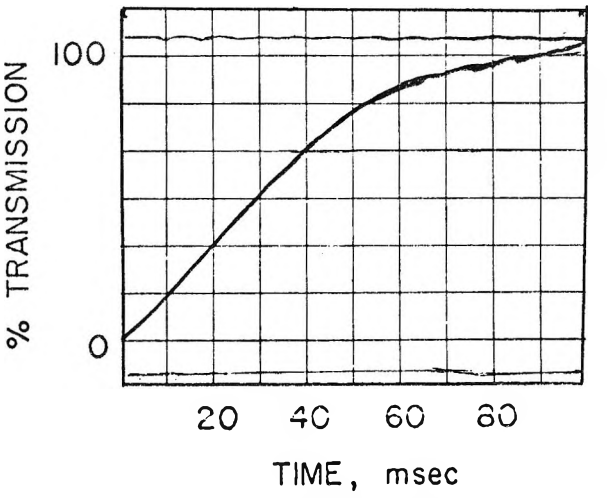


Figure 2. Plot of percent transmission vs. time for the reaction of 0.13 M *n*-butyllithium with 1.3×10^{-3} M 4-methylmercaptoacetophenone in benzene at 25.0 °C, recorded at 330 nm.

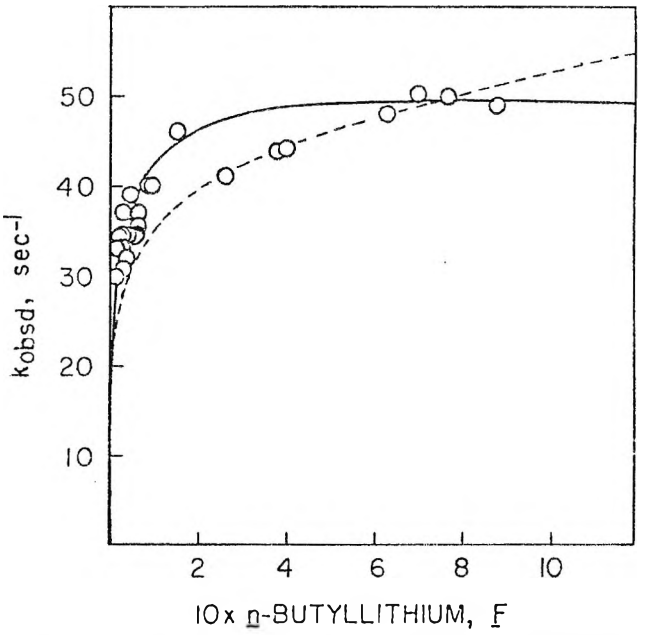


Figure 3. Plot of observed pseudo-first-order rate constant vs. *n*-butyllithium for the reaction of *n*-butyllithium with 1.22 to 2.28×10^{-3} M 4-methylmercaptoacetophenone in benzene at 25.0 °C, Table II. The solid line is calculated from eq 7 with $K_1 = 600$ and $k_1 = 50$. The dotted line is calculated from eq 4 with $k_2K_2 = 70$.

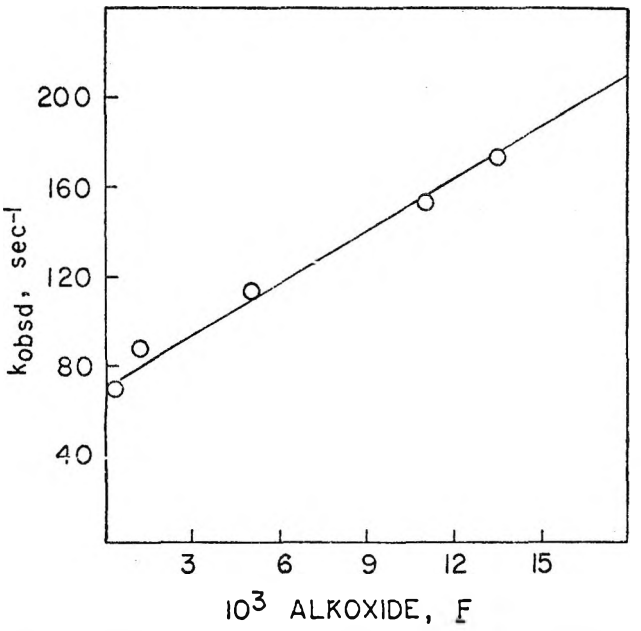


Figure 4. Plot of observed rate constant vs. the concentration of lithium 2-(4-methylmercaptophenyl)-2-hexoxide for the reaction of 0.15 M *n*-butyllithium with 5.75×10^{-4} M 4-methylmercaptoacetophenone, in the presence of lithium 2-(4-methylmercaptophenyl)-2-hexoxide, in benzene at 25.0 °C.

0.1 s at room temperature, which is slow compared to the rate of addition of *n*-butyllithium to ketone 2. However, it is clear that more information on the composition and rates of equilibration of *n*-butyllithium solution containing alkoxides is needed to further clarify the course of the reaction.

The products of the reaction of 4-methylmercaptoacetophenone with *n*-butyllithium were analyzed under conditions employed in the kinetic study. A sample of ketone 2, containing biphenyl as an internal standard, was mixed with *n*-butyllithium in benzene in a stopped-flow apparatus. The stopped-flow effluent was quenched with ice, acidified to pH 7, then analyzed by GLC. The GLC chromatogram consisted of three peaks with retention times identical with those of the addition alcohol, 2-(4-methylmercaptophenyl)-2-hexanol, and small amounts of the alcohol dehydration products, 2-(4-methylmercaptophenyl)-2-hexene and 2-(4-methylmercaptophenyl)-1-hexene. The pinacol of ketone 2, which was not eluted from the GLC column, was not detected by thin layer chromatography, indicating that less than 1.5% of the pinacol was present since 1.5% of the pinacol in a control sample was detected.

Product studies of the reaction of *n*-butyllithium–alkoxide mixtures with 4-methylmercaptoacetophenone and of the reaction of *n*-butyllithium with 4-methylmercaptoacetophenone containing product alcohol were performed under the reaction conditions employed in the kinetic studies. In all cases, only the addition product alcohol, 2-(4-methylmercaptophenyl)-2-hexanol, was found by GLC analysis, using biphenyl as the internal standard.

Experimental Section

***n*-Butyllithium.** *n*-Butyllithium was prepared from Foote Mineral Co. Reactor Grade lithium (99.99% Li) and degassed freshly distilled *n*-butyl chloride on a vacuum line that was under a positive pressure of argon. Lithium chips were cut in an argon atmosphere, under mineral oil, and then the oily pieces were transferred to the vacuum line. After evacuating and flushing the vacuum line with argon, the lithium chips were washed three times with benzene solution, and the washings were expelled from the vacuum line. Fresh benzene was admitted to the reaction vessel and the halide was slowly added over ca. 1 h, while the reaction was maintained at room temperature. The reaction mixture was allowed to stir for ca. 12 h after the halide addition was complete. The reagent was filtered twice through glass fritted filters and transferred via argon pressure into silicon rubber septum topped vials. The samples were used within 2 h after they were removed from the vacuum line, and titrated within 8 h after use.

Table IV. Summary of Observed Pseudo-First-Order Rate Constants for the Reaction of 0.15M *n*-Butyllithium with 5.8×10^{-4} M 4-Methylmercaptoacetophenone in the Presence of Lithium 2-(4-Methylmercaptophenyl)-2-hexoxide, in Benzene at 25.0° C

10^3 alkoxide, M	k_{obsd}, s^{-1}
0.35	70
1.2	88
5.0	113
11.0	153
13.5	174

Table V. Effect of Product Alkoxide on the Reaction of 0.151 M *n*-Butyllithium with 10^{-3} M 4-Methylmercaptoacetophenone in Benzene at 25.0°C

10^3 alkoxide[a]	k_{obsd}, s^{-1}
1.27	50
2.23	56
5.97	53
9.68	54

[a] Alkoxide formed by reaction of 2-(4-methylmercaptophenyl)-2-hexanol, contained in the ketone solution, with *n*-butyllithium in the stopped-flow apparatus.

n-Butyllithium reagents were analyzed by total base titration with standard standardized hydrochloric acid solutions. The lithium reagent content, analyzed with standard solutions of *sec*-butyl alcohol in xylene containing 1,10-phenanthroline as an indicator, agreed with the total base titer. Tared vials used in kinetic experiments were weighed to determine the amount of *n*-butyllithium–benzene solution they contained. Then the titration mixture, which was stored under argon, was admitted to vials via a syringe needle on a microburet. A red-orange alkyllithium indicator complex forms and when all lithium reagent has been converted to lithium *sec*-butoxide, the solution becomes lime green.[33]

Alkoxide concentrations were calculated from the weight of alcohol added to the reagent vials. The alcohols were vacuum dried for at least 1 day before *n*-butyllithium solutions were added.

4-Methylmercaptoacetophenone. The preparation of 4-methylmercaptoacetophenone has been described elsewhere.[29] Alternatively,[34] the ketone was prepared by placing 0.26 mol (31 ml) of thioanisole and 0.48 mol (100 g) of trifluoroacetic anhydride in a 1-l. flask equipped with magnetic stirrer, condenser, addition funnel, and nitrogen inlet. The flask was cooled in an ice bath and 0.38 mol (23 ml) of acetic acid was added. The mixture was extracted with ether, and the ether was subsequently washed with bicarbonate and water. The ether was dried over sodium sulfate and removed from the product on a rotary evaporator. The resulting orange crystals were purified by distillation at 125 °C and 0.05 mm pressure. The white, crystalline distillate was recrystallized once from hexane, giving 22.1 g of crystals (51%), mp 80.5–81.5 °C.

The concentrations of ketone samples used in kinetic studies were calculated from the weight of ketone and the weight of added solvent. The ketone dried on a vacuum line (0.05 mm) for at least 1 day before freshly distilled solvent was added to the vials.

2,3-Dimethyl-4′-methylmercaptobenzophenone. The preparation of 2,4-dimethyl-4′-methylmercaptobenzophenone has been described elsewhere.[29c]

2-(4-Methylmercaptophenyl)-2-hexanol. A 2-l. flask was equipped with a magnetic stirrer, syringe port, dropping funnel, condenser, and argon inlet. Benzene (350 ml) dried over 4-A molecular sieves, was added to the flask; then 150 ml of 1.3 N *n*-butyllithium in hexane (Foote Mineral Co.) was added through the syringe port. Ten grams of 4-methylmercaptoacetophenone in 200 ml of benzene was added to the flask over a 45-min period. After standing overnight the reaction mixture was quenched with water and neutralized with dilute sulfuric acid. The layers were separated, and the hydrocarbon layer was washed with 2 × 50 ml of

aqueous potassium carbonate solution and 3 × 150 ml of water and dried over sodium sulfate. The solvent was removed on a rotary evaporator, yielding a viscous brown oil. Distillation at 0.75 mm through a short-path micro distillation head yielded 7 ml of a pale yellow oil containing some starting ketone, and 3 ml of oil free of ketone: ir (CCl_4) 3430 cm^{-1} (–OH); NMR (CCl_4) δ 7.15 (m, 4, Ar), 2.6 (s, 1, –OH), 2.32 (s, 3, CH_3S–), 0.6–1.9 (m, 12, alkyl). Anal. Calcd for $C_{13}H_{20}OS$: C, 69.50; H, 8.99; S, 14.29. Found: C, 68.94; H, 8.95; S, 13.87.

2,3-Di(4-methylmercaptophenyl)-2,3-butanediol. 4-Methylmercaptoacetophenone (10 g) was dissolved in 75 ml of absolute ethanol and 50 ml of benzene. Aluminum foil (3 g), cut in 0.5-in. squares, was added to the solution. Mercuric chloride (0.15 g) was added to the mixture, and then the reaction mixture was stirred and cooled to ice-bath temperature as described by Sisido and Nozaki.[35]

The flask was allowed to warm, and an exothermic reaction began, causing the reaction to reflux for approximately 1 h. The mixture was heated to reflux for an additional 1 h. The resulting gray viscous mixture was poured onto ice and neutralized with dilute hydrochloric acid. The benzene layer was separated from the aqueous phase, combined with benzene extracts of the aqueous phase, and dried over sodium sulfate. The solvent was removed on a rotary evaporator. The resulting solid was recrystallized twice from benzene (69% yield): mp 127–129; ir (CCl_4) 3600 cm^{-1} (–OH); NMR (CCl_4) δ 7.08. Anal. Calcd for $C_{18}H_{22}O_2S_2$: C, 64.63; H, 6.63; S, 19.17; O, 9.57. Found: C, 64.36; H, 6.45; S, 19.24; O, 9.95 by difference.

Product Studies. A 1.8×10^{-2} M solution of 4-methylmercaptoacetophenone in benzene, containing biphenyl in the molar ratio ketone/biphenyl 1.23, was mixed with a 0.27 M solution of *n*-butyllithium in a stopped-flow apparatus. The effluent of the stopped-flow instrument was quenched with ice so that the time of reaction was less than 1 min. The ice–benzene mixture was warmed to room temperature and titrated to pH 6 with dilute sulfuric acid. The benzene layer was then separated, combined with an ether extract of the aqueous phase, and dried over sodium sulfate. Solvent was removed by gently boiling off ether on a steam bath, then by bubbling dry nitrogen through the solution overnight. Quantitative GLC analysis, with biphenyl as the standard, on a 2-m 20% Carbowax 20M on Chromosorb W column indicated that the addition product was formed in 99% yield. Less than 1% of the addition product had dehydrated. No evidence for ketone reduction or enolization was found by this procedure, placing the limits of these products at 2%. No evidence for ketone dimerization product was found when the reaction product was analyzed on a 2-m, 1.5% SE-30 on Fluorapak 80 column or by thin layer chromatography. The limit of detection by the TLC method was ca. 1.5%. A 10^{-2} M ketone solution, containing triphenylmethanol in the ratio ketone/Ph_3COH 2.595, was treated with 0.18 M *n*-butyllithium solution. GLC analysis indicated that only addition product was formed. Similarly, a 10^{-2} M ketone solution containing the ketone dimerization product in the ratio ketone/pinacol 71.24 was found to yield only addition product. A 10^{-2} M ketone solution was allowed to react with a 0.18 M *n*-butyllithium solution that was saturated with the lithium salt of triphenylmethanol and found to yield only addition product.

Kinetics and Spectroscopy. The two uv stopped-flow spectrophotometers with dead times of 0.03 and 0.001 s as well as the rapid-scan spectrometer have been described elsewhere.[2,29b] The stopped-flow ir spectrophotometric experiments were performed with the apparatus previously described;[29a] however, the ir chopping frequency has been increased to ca. 10 000 Hz.

Registry No.—2, 1778-09-2; 2-(4-methylmercaptophenyl)-2-hexanol, 57560-00-6; *n*-butyllithium, 109-72-8; 2,3-di(4-methylmercaptophenyl)-2,3-butanediol, 57560-01-7; benzene, 71-43-2.

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Mesoionic Compounds. XXXV. Cycloaddition Reactions of the *anhydro*-4-Hydroxythiazolium Hydroxide and *anhydro*-5-Hydroxyoxazolium Hydroxide Systems with Heterocumulenes[1]

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Activated isocyanates underwent ready reaction at room temperature with *anhydro*-2-*p*-chlorophenyl-4-hydroxy-3-phenylthiazolium hydroxide yielding 1:1 primary cycloadducts assigned a 2,6-diaza-7-thiabicyclo[2.2.1]-heptane structure. Analogous adducts were also obtained with *anhydro*-5-hydroxy-3-methyl-2-phenyloxazolium hydroxide. Phenyl isocyanate and phenyl isothiocyanate, however, required elevated temperatures (80 °C) for the formation of 1:1 adducts with the former system.

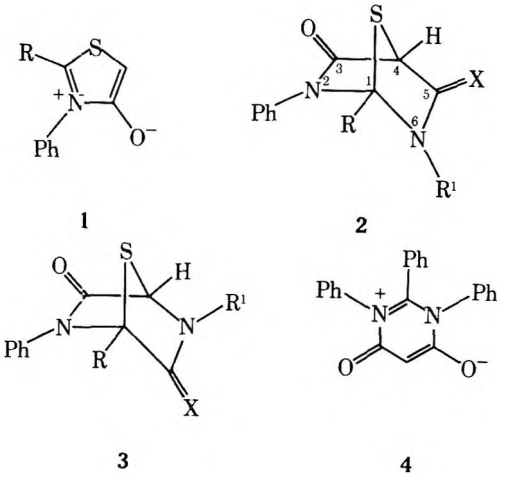
Heterocumulenes have been shown to undergo a variety of cycloaddition reactions[2] and, with the mesoionic *anhydro*-5-hydroxythiazolium hydroxide system, provided several interesting 1:1 cycloadducts as well as a convenient route to the *anhydro*-4-mercaptoimidazolium hydroxide system.[3] We now describe the reactions of several isocyanates and isothiocyanates with the isomeric *anhydro*-4-hydroxythiazolium hydroxide system **1** and with the *anhydro*-5-hydroxyoxazolium hydroxide system **10**, the adducts from the latter being particularly interesting in that they retain the elements of carbon dioxide, an unusual feature in products derived from this ring system.[4]

Phenyl isothiocyanate, phenyl isocyanate, benzoyl isocyanate, *p*-chlorobenzoyl isocyanate, trichloroacetyl isocyanate, *p*-toluenesulfonyl isocyanate, and *N*-chlorosulfonyl isocyanate all underwent ready reaction with *anhydro*-2-aryl-4-hydroxy-3-phenylthiazolium hydroxide[5] (**1**, R = Ph and *p*-ClC_6H_4) forming crystalline cycloadducts. Analytical and mass spectral data (Table I) established that these were 1:1 adducts, and structural formulas have been assigned on the basis of the following considerations.

With phenyl isothiocyanate and **1** (R = Ph) an orange-yellow, crystalline product (Table I) separated from the hot benzene reaction mixture after 15 min. Its molecular formula, $C_{22}H_{16}N_2OS_2$, corresponded to a simple 1:1 adduct but the spectral data excluded any substitution into the 5 position of **1**. Its infrared spectrum, devoid of OH, SH, or NH absorptions, showed ν_{CO} 1630 cm^{-1} and $\nu_{C=S}$ 1135 cm^{-1}, and the ultraviolet spectrum [203 nm (log ϵ 4.65), 277 (4.10), 306 sh (3.85), 424 (4.06)] showed a considerable shift to longer wavelength from that of **1** (R = Ph), and also from the absorption of an *N*-phenylthioamide such as *N*-phenylthioacetamide[6] [218 nm (log ϵ 4.15), 301 (4.01)]. The NMR spectrum was very simple, consisting of aromatic protons (15) at δ 7.63 and a singlet proton at an exceptionally low chemical shift, δ 12.06.

Several structural representations for an adduct of this composition are possible, including those containing an SH or OH group, but all may be excluded on the basis of the above spectral data except **2** and **3** (R = R^1 = Ph; X = S), representing different modes of addition of phenyl isothiocyanate to the thiocarbonyl ylide dipole of **1**. Structure **3** can be discarded, as in the corresponding adduct from **1** (R = Ph) and phenyl isocyanate, the singlet proton moved upfield, albeit still at an exceptionally low value, to δ 10.27. This indicates that the bridgehead proton at C-4 is being strongly deshielded by the C=O and the C=S groups at the 3 and 5 positions, respectively, being in the deshielding zone of both groups. As the C=S group is known[7] to exert a stronger deshielding influence than the C=O group, such a shift is consistent with structure **2**, 3-oxo-1,2,6-triphenyl-2,6-diaza-7-thiabicyclo[2.2.1]heptane-5-thione (R = R^1 = Ph; X = S).

A low chemical shift in the region of δ 12.06 is usually associated with a proton attached to an electronegative element such as oxygen, nitrogen, or sulfur, or to an aldehydic proton. In **2**, the 4 proton is not readily exchanged with deuterium, requiring base catalysis for exchange to occur.



1 **2**

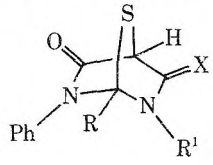
3 **4**

The inductive effects exerted by the carbonyl groups and thiocarbonyl groups, as well as the bridgehead sulfur atom, alone cannot account for this low chemical shift. In similar cycloadducts obtained from heterocumulenes and *anhydro*-1,3-dimethyl-4-hydroxy-1,2,3-triazolium hydroxide,[8] *anhydro*-2,3-diphenyl-4-hydroxy-1-methylimidazolium hydroxide,[3] and *anhydro*-5-hydroxy-3-methyl-2-phenylthiazolium hydroxide,[3] similar chemical shifts were observed for the analogous bridgehead hydrogen atoms.

The ultraviolet spectrum of **2** (R = R^1 = Ph; X = S) is also consistent with this structure. Interaction between a β-thio group and a carbonyl group has been shown[9] and in β-keto sulfides causes a shift of the perturbed CO absorption to 300 nm.,[10] and interaction between the bridge sulfur atom and the thiocarbonyl group also explains unsuccessful attempts to remove cleanly the sulfur bridge (see below).

Phenyl isocyanate and **1** (R = Ph) readily formed a yellow 1:1 cycloadduct (Table I) over 1 hr in refluxing benzene. Its spectral characteristics are consistent with structure **2** (R = R^1 = Ph; X = O). The infrared spectrum showed ν_{CO} 1650 and 1625 cm^{-1}, the latter most likely the result of interaction of the sulfur bridge with one of the carbonyl groups, an effect which is also reflected in the ultraviolet spectrum having a long wavelength absorption at 400 nm. The NMR spectrum, in addition to the aromatic

Table I. Cycloadducts Obtained from Heterocumulenes and the *anhydro*-4-Hydroxythiazolium Hydroxide System[a]

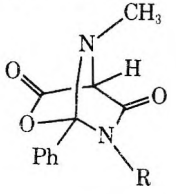


Registry no.	R	R¹	X	Yield, %	Mp,[b] °C	Molecular formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Spectral data: M·⁺ (rel intensity)	Ir (KBr), cm⁻¹	λ_{max} (CH_3OH), nm (log ε)	NMR, δ
57513-19-6	Ph	Ph	S	88	230[c]	$C_{22}H_{16}N_2OS_2$	68.03	4.15	7.21	67.99	3.99	7.19	388 (65)	1630 (CO), 1135 (CS)	203 (4.65), 277 (4.10), 306[d] (3.85), 424 (4.06)	12.06 (s, 1, H_4), 7.63 (m, 15, aromatic)[e]
57513-20-9	Ph	Ph	O	73	215–216[f]	$C_{22}H_{16}N_2O_2S$	70.96	4.33	7.52	71.24	4.33	7.69	372 (17)	1650, 1625 (CO)	203 (4.58), 234 (4.20), 268 (4.15), 400 (4.20)	10.27 (s, 1, H_4), 7.40 (m, 15, aromatic)[e]
57513-21-0	*p*-ClC_6H_4	PhCO	O	74	273–276	$C_{23}H_{15}ClN_2O_3S$	63.52	3.48	6.44	62.57	3.52	6.18	434 (6)	1740, 1690, 1640 (CO)	225 (4.33), 245[d] (4.25), 399 (4.04)	8.3–7.2 (m, H_4 and aromatic)[g]
57513-22-1	*p*-ClC_6H_4	SO_3Et	O	61	184–187	$C_{18}H_{15}ClN_2O_5S_2$	49.25	3.44	6.38	49.14	3.43	6.38		1700, 1650 (CO)	260 (4.15), 285[d] (3.86), 411 (4.13)	1.3 (t, 3, $SO_3CH_2CH_3$), 4.3–4.4 (dq, 2, SO_3CH_2-CH_3), 7.4–7.5 (bs, 9, aromatic), 9.8 (s, 1, H_4)[h]
57513-23-2	*p*-ClC_6H_4	*p*-$CH_3C_6H_4SO_2$	O	36	252–257	$C_{27}H_{17}ClN_2O_4S_2$	56.96	3.53	5.78	57.05	3.47	5.66	485 (3)	1660, 1640 (CO), 1350, 1170 (SO_2)	223 (3.82), 259 (3.79), 395 (3.75)	2.4 (s, 3, CH_3), 7.0–8.1 (m, 13, aromatic), 10.8 (s, 1, H_4)[e]
57513-24-3	*p*-ClC_6H_4	*p*-ClC_6H_4CO	O	74	273–275	$C_{23}H_{14}Cl_2N_2O_3S$	58.85	3.01	5.97	59.15	2.94	5.84	469 (9)	1730, 1680, 1630 (CO)	232 (4.32), 254 (4.32), 399 (4.16)	7.00–8.17 (m, H_4 and aromatic)[g]
57513-25-4	*p*-ClC_6H_4	Cl_3CCO	O	92	250[i]	$C_{18}H_{10}Cl_4N_2SO_3$	45.38	2.11	5.88	45.02	2.21	5.69		1760, 1680, 1625 (CO)		12.43 (s, 1, H_4), 7.60–7.22 (m, 9, aromatic)[j]

57513-26-5	*p*-ClC_6H_4	H	O	80	279–280[k]	$C_{16}H_{11}ClN_2SO_2$	58.08	3.35	8.47	57.99	3.34	8.50	330 (20)	3375 (NH), 1640, 1575 (CO)	7.54–7.30 (m, aromatic)[h]
57513-27-6	*p*-ClC_6H_4	CH_3CO	S	90	217–218[l]	$C_{18}H_{13}ClN_2S_2O_2$	55.59	3.34	7.20	55.47	3.37	7.22	338 (45)	1720, 1650 (CO)	12.0 (broad s, 1, H_4), 7.8–7.1 (m, 9, aromatic), 2.4 (s, 3, CH_3)[e]

[a] All crystallized from chloroform–ether as yellow needles except *c*, orange yellow needles, and *i*, bright yellow irregular prisms from 1,2-dichloroethane, *k*, orange prisms from ethanol, and *l*, lustrous red prisms from chloroform–ether. [b] Decomposition. [d] Shoulder. [e] $CDCl_3$. [f] Chromatography on Kieselgel g using $CHCl_3$. as eluent was needed for purification. [g] CF_3CO_2D. [h] Me_2SO-d_6. [i] CF_3COOH.

Table II. 1:1 Primary Cycloadducts Derived from *anhydro*-5-Hydroxy-3-methyl-2-phenyloxazolium Hydroxide and Activated Isocyanates[a]



Registry no.	R	Mp, °C (dec)	Yield, %	Habit	Formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Spectral data: ν_{CO}, cm^{-1} (KBr)	Spectral data: λ_{max} (CH_3OH), nm (log ϵ)	Spectral data: NMR ($CDCl_3$), δ
57513-28-7	PhCO	193–196	16	Yellow irreg prisms	$C_{18}H_{14}N_2O_4$[b]	67.07	4.38	8.69	67.01	4.35	8.62	1720, 1700–1690	323 (3.75), 259[c] (4.05), 240 (4.42)	10.95 (bs, 1, C_4 H, exchanged with D_2O), 7.27–8.13 (m, 10, aromatic), 4.27 (s, 3, NCH_3)
57513-29-8	*p*-ClC_6H_4CO	209–211	60	Yellow needles	$C_{18}H_{13}ClN_2O_4$	60.60	3.67	7.85	60.39	3.64	7.82	1720, 1700 (b)	330 (3.76), 263[c] (4.21), 246 (4.42)	10.90 (bs, 1, C_4 H, exchanged with D_2O), 7.27–8.02 (m, 9, aromatic), 4.27 (s, 3, NCH_3)
57513-30-1	*p*-$CH_3C_6H_4SO_2$	189–192	68	Colorless prisms	$C_{18}H_{16}N_2O_5S$	58.05	4.33	7.52	58.18	4.24	7.51	1710, 1680	230 (4.23)	9.80 (bs, 1, C_4 H, exchanged with D_2O), 7.27–8.10 (m, 9, aromatic), 4.13 (s, 3, NCH_3), 2.45 (s, 3, aryl CH_3)

[a] All recrystallized from 1,2-dichloroethane. [b] $M^{\cdot+}$ 322 (3). [c] Shoulder.

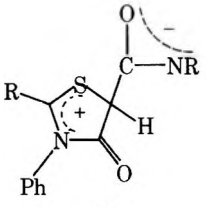
protons at δ 7.40, consisted of a sharp singlet at δ 10.27 which required base catalysis for deuterium exchange.

An immediate reaction was observed when benzoyl isocyanate and 1 (R = p-ClC_6H_4) were mixed in dry benzene at room temperature, a 1:1 cycloadduct being obtained as yellow needles (Table I). The infrared spectrum showed carbonyl absorptions at 1740 (COPh), 1690 (CON<), and 1640 cm^{-1} (CON<), the ultraviolet spectrum a long-wavelength absorption at 399 nm, but in this case the chemical shift of the bridgehead proton, characteristic of the above adducts, was not observed owing to use of CF_3CO_2H as the NMR solvent. These data are best accommodated by structure 2 (R = Ph; R^1 = COPh; X = O).

An equally ready reaction was observed between 1 (R = p-ClC_6H_4) and N-chlorosulfonyl isocyanate. This adduct, obtained as an unstable, hygroscopic, greenish solid, was converted into the corresponding ethyl ester which was isolated as yellow needles (Table I). Two carbonyl absorptions at 1700 and 1650 cm^{-1}, and a long-wavelength ultraviolet absorption at 411 nm, are consistent with the spectral parameters associated with the structure 1-p-chlorophenyl-6-ethoxysulfonyl-2-phenyl-2,6-diaza-7-thiabicyclo-[2.2.1]heptane-3,5-dione (2, R = p-ClC_6H_4; R^1 = SO_2Et; X = O). The NMR spectrum, in addition to the aromatic protons and those of an OEt group, showed a singlet at δ 9.8, assignable to the C-4 bridgehead proton.

p-Toluenesulfonyl isocyanate also readily formed a 1:1 cycloadduct with 1 (R = p-ClC_6H_4) in dry benzene at room temperature within 5 min. This yellow product's spectral characteristics (Table I) are fully in accord with its representation as 1-p-chlorophenyl-2-phenyl-6-p-tolylsulfonyl-2,6-diaza-7-thiabicyclo[2.2.1]heptane-2,5-dione (2, R = p-ClC_6H_4; R^1 = p-$CH_3C_6H_4SO_2$; X = O).

The data described above indicate 2 as the structure for these cycloadducts, a possible alternative ylidic structure 5 that cannot be definitely excluded on the basis of these data being eliminated on the basis of ^{13}C NMR and chemical data. The ylide 5 is plausible for the 1:1 adduct, being



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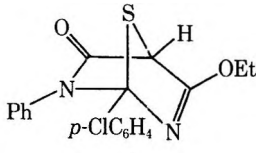

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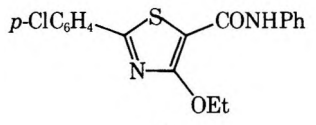

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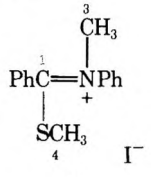

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analogous to a similar type betaine 1:1 complex postulated[11] in the reaction of pyridine N-oxide with sulfonyl diisocyanate, and it should readily undergo protonation with perchloric acid, or alkylation with suitable reagents, in analogy with similar N-imines and C-ylides derived from 1,2,4-triazole[12] and other such systems. The adducts described above were remarkably inert to protonation and alkylation. In particular the p-toluenesulfonyl isocyanate adduct did not react with perchloric acid, methyl iodide, triethyloxonium fluoroborate, and methyl trifluoromethanesulfonate and on the basis of these results the ylide structure 5 must be discarded.

The p-toluenesulfonyl derivative was inert to m-chloroperbenzoic acid, sulfoxide formation not being observed, although it would be expected that in structure 2 (R = p-ClC_6H_4; R^1 = p-$CH_3C_6H_4SO_2$) with a sulfide bridge, oxidation would occur readily as has been observed with the 1:1 adducts derived from these mesoionic systems and several olefins.[13] The spectral data for these compounds described above, however, reflect the unusual nature of the adducts in that the lone pair electrons on the bridge sulfur atom are not readily available for reaction with oxidizing agents.

A major premise in our structural arguments is that the bridgehead proton at C-4 is strongly deshielded by the C-3 carbonyl group and the C-5 carbonyl or thiocarbonyl group. Accordingly, change in the nature of the group at C-5 should have a pronounced effect on the chemical shift of this bridgehead proton as well as on the properties of the system, and it was found that the 1:1 cycloadduct obtained from 1 (R = p-ClC_6H_4) and trichloroacetyl isocyanate was a particularly useful substrate upon which to bring about the desired transformations.

Hydrolysis of the adduct 2 (R = p-ClC_6H_4; R^1 = $COCCl_3$; X = O), formed at room temperature in 92% yield, with hot aqueous sodium carbonate solution over 15 min gave a product 2 (R = p-ClC_6H_4; R^1 = H; X = O) in 80% yield which, with Meerwein's reagent, afforded 1-p-chlorophenyl-3-ethoxy-6-phenyl-2,6-diaza-7-thiabicyclo[2.2.1]-hept-2-en-5-one (6). Thermolysis of 6 at 170 °C (0.5 mm) could have resulted in extrusion of sulfur or elimination of phenyl isocyanate, the latter being anticipated on the basis of the behavior of the initial cycloadducts of this ring system with acetylenic dipolarophiles.[5] Two products were isolated from the thermolysis, identified as 2 (R = p-ClC_6H_4; R^1 = H; X = O) and 2-p-chlorophenyl-4-ethoxythiazole-5-carboxanilide (7). Analytical and spectral data substantiating the above structures are shown in Table I and the Experimental Section. The trichloroacetyl group in 2 (R = p-ClC_6H_4; X = O) was necessary for this facile hydrolysis to occur. The adduct 2 (R = p-ClC_6H_4; R^1 = $COCH_3$; X = S), obtained from 1 (R = p-ClC_6H_4) and acetyl isothiocyanate, could not be hydrolyzed except under conditions that resulted in a more deep-seated degradation of the adduct.

The variation of the chemical shift of the bridgehead proton at C-4 in this series of products is particularly informative. In 2 (R = p-ClC_6H_4; R^1 = $COCCl_3$; X = O) a singlet proton at δ 12.43 may be attributed to the bridgehead proton; conversion of this adduct into 2 (R = p-ClC_6H_4; R^1 = H; X = O) resulted in this proton being obscured by the aromatic protons (δ 7.5–7.3), there being a complete absence of a signal at lower field. This large chemical shift may be due in part to an appreciable contribution from the enolic form of the newly generated amide. A further upfield shift occurs on formation of 6. No signal was found in the region δ 18–10 but a one-proton singlet occurred at δ 7.10. Although this signal cannot be assigned with absolute certainty, there are strong indications that it can be assigned to the bridgehead proton at C-4. The NMR spectrum of the thermolysis product 7 also showed an interesting feature. The 4-ethyl group gave rise to two quartets at δ 3.8 and 3.1 (J = 8.0 Hz) that collapsed to two singlets on irradiation of the triplet resonance, and this nonequivalency of the methylene protons was no doubt due to a steric interaction with the neighboring 5-carboxanilide group.

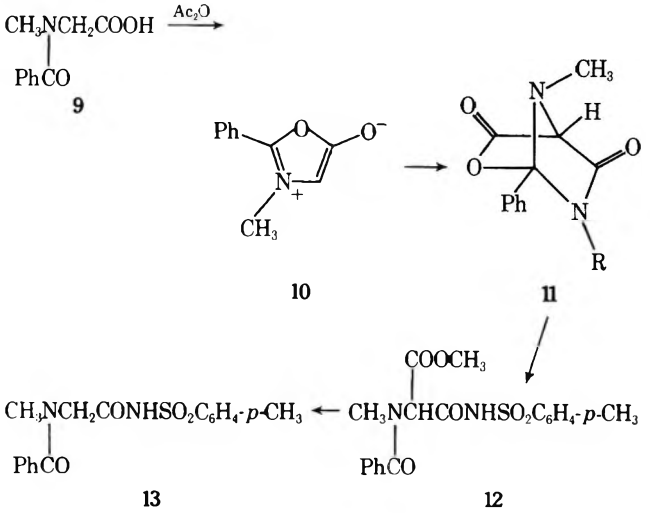
The ^{13}C NMR spectra of several of these products were also helpful in these structural studies, particularly in providing additional evidence for the elimination of the ylide structure 5 for these cycloadducts. The ylide structure requires the presence of a >C=N⁺< entity with the carbon being attached to an aromatic ring and a sulfur atom. Such a partial structure is present in the S-methylthioamide[14] derivative 8 and the carbon chemical shift in this product

Table III. ^{13}C Chemical Shifts for Several Heterocumulene Cycloadducts (ppm Downfield from Me_4Si)

Compd	Carbon atom number					
	1	3	4	5	8	9
2, R = *p*-ClC_6H_4; R^1 = $COCH_3$; X = S	125.78	156.83	110.34	184.52	169.41	25.87
6	125.96	137.62	88.72	156.83	60.48	14.04
11, R = *p*-ClC_6H_4CO	120.61	161.75	92.85	163.63	36.43	157.35
8	194.04	48.74	18.10			

was observed at 194.04 ppm. In *anhydro*-5-hydroxy-3-methyl-2-phenylthiazolium hydroxide the analogous carbon atom (C-2) was observed at 141.3 ppm and in *anhydro*-2-ethyl-5-mercapto-3-phenyl-1,3,4-thiadiazolium hydroxide the analogous carbon had shifted to 173.8 ppm.[15] These spectral data, as well as the chemical transformations above, clearly establish the bicyclic structure **2** for these heterocumulene cycloadducts.

In the reaction of *anhydro*-5-hydroxy-3-methyl-2-phenyloxazolium hydroxide (**10**) with *p*-toluenesulfonyl, benzoyl, and *p*-chlorobenzoyl isocyanate, the mesoionic system[3,4] was generated in situ from *N*-benzoylsarcosine (**9**) and acetic anhydride at 40 °C. These all formed 1:1 cycloadducts,



described in Table II, and assigned structure **11** (R = *p*-$CH_3SO_2C_6H_4$, COPh, and *p*-ClC_6H_4CO) on the basis of the spectral data and by analogy with the adducts discussed above. A similar product has been obtained from *anhydro*-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide and phenyl isocyanate.[16]

The above adducts (Table II) decomposed with gas evolution at their melting points and on electron impact the predominant fragmentation pathway was a disassociation process. Refluxing **11** (R = *p*-$CH_3SO_2C_6H_4$) with methanol resulted in an hydrolysis product **12** and use of warm 10% sodium hydroxide solution as the hydrolysis medium gave **13**, which was also obtained from **12** and 10% sodium hydroxide solution.

Just as some five-membered mesoionic systems can be converted into other representatives of this class of compounds by reaction with phenyl isothiocyanate,[8] removal of the sulfur bridge in **2** (R = R^1 = Ph; X = O) would provide a simple route to *anhydro*-4-hydroxy-6-oxo-1,2,3-triphenylpyrimidinium hydroxide[17] (**4**). However, all attempts to remove the sulfur with reagents such as triphenylphosphine, tris(dimethylamino)phosphine, Raney nickel, etc., were unsuccessful, probably reflecting the interaction of the sulfur with the C-3 or C-5 carbonyl groups. Oxidation with peracetic acid was successful, but, in this case, the product obtained was PhNHCOCHOHCOPhCOPh, formed by hydrolysis of **4** under the reaction conditions.[18]

Experimental Section[19]

Reaction of ***anhydro*-4-Hydroxy-2,3-diphenylthiazolium Hydroxide with Phenyl Isothiocyanate (and Phenyl Isocyanate).** The mesoionic compound[5] **1** (R = Ph) (2.2 g, 0.087 mol) and phenyl isothiocyanate (1.5 g, 0.011 mol) in dry benzene (100 ml) were heated together under reflux and, within 15 min, product started to separate. After an additional 1 h, the reaction mixture was cooled, anhydrous ether added, and the product collected. 3-Oxo-1,2,6-triphenyl-2,6-diaza-7-thiabicyclo[2.2.1]heptane-5-thione (**2**, R = R^1 = Ph; X = S) crystallized from chloroform–ether as orange-yellow needles, 88%, mp 230 °C dec (Table I). Acetyl isothiocyanate[20] and **1** (R = *p*-ClC_6H_4) required a 3-h reflux period and, on cooling, red prisms of the adduct separated, mp 217–218 °C.

General Procedure for the Reaction of *anhydro*-2-*p*-Chlorophenyl-4-hydroxy-3-phenylthiazolium Hydroxide (1, R = *p*-ClC_6H_4) and Activated Isocyanates. The mesoionic compound and a slight excess of the isocyanate were mixed in benzene with stirring at room temperature. After several minutes the products separated and were collected and recrystallized from chloroform–ether (Table I).

With *N*-chlorosulfonyl isocyanate the precipitated product was extremely unstable and it was converted into the corresponding ester by the addition of excess ethanol.

Hydrolysis of 1-*p*-Chlorophenyl-2-phenyl-6-trichloroacetyl-2,6-diaza-7-thiabicyclo[2.2.1]heptane-3,5-dione (2, R = *p*-ClC_6H_4; R^1 = $COCCl_3$; X = O). The adduct (4.76 g, 0.01 mol) was heated under reflux with aqueous sodium carbonate (4 g in 40 ml of H_2O) for 15 min. On cooling, an orange solid separated that crystallized from absolute ethanol as orange prisms and was identified as **2** (R = *p*-ClC_6H_4; R^1 = H; X = O), 2.7 g (80%), mp 279–280 °C dec (Table I).

1-*p*-Chlorophenyl-3-ethoxy-6-phenyl-2,6-diaza-7-thiabicyclo[2.2.1]hept-2-en-5-one (6). A slurry of **2** (R = *p*-ClC_6H_4; R^1 = H; X = O) (3.30 g, 0.01 mol) in dry methylene chloride (100 ml) was treated with triethyloxonium fluoroborate[21] (1.90 g, 0.01 mol) added in one portion and, after 2 h, a homogeneous solution had formed. After addition of aqueous potassium carbonate (5.6 g of 50% solution), the organic portion was separated and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo afforded an orange oil that crystallized from ether–pentane as orange prisms: 2.25 g (62%); mp 88°; ir (KBr) 1650 (CO), 1600 cm^{-1} (C=N); NMR ($CDCl_3$, 100 MHz) δ 7.5–7.2 (m, 8, aromatic), 7.1 (s, 1, H_4), 4.5 (qt, 2, CH_2CH_3, J = 7.0 Hz), 1.4 (t, 3, CH_2CH_3); M$^+$· 358 (20).

Anal. Calcd for $C_{18}H_{15}ClN_2SO_2$: C, 60.21; H, 4.21; N, 7.80. Found: C, 59, 99; H, 4.30; N, 7.69.

Thermolysis of 6. The above 3-ethoxy compound (400 mg) was heated at 170 °C (0.5 mm). On cooling, the crude melt was dissolved in acetone and purified by chromatography on preparative silica gel (0.5 mm) using ethyl acetate. Crystallization of the first band from 1,2-dichloroethane afforded 1-*p*-chlorophenyl-2-phenyl-2,6-diaza-7-thiabicyclo[2.2.1]heptane-3,5-dione (**2**, R = *p*-ClC_6H_4; R^1 = H; X = O) as yellow prisms, 100 mg (ca. 10%), mp 280 °C. The second major band crystallized from ether–pentane as orange prisms and was identified as 2-*p*-chlorophenyl-4-ethoxythiazole-5-carboxanilide (**7**): 210 mg (50%); mp 222°; ir (KBr) 3325 (NH), 2975 (aromatic CH), and 1625 cm^{-1} (CO); NMR ($CDCl_3$) δ 8.0 (broad s, 1, NH), 7.5–7.0 (m, 9, aromatic), 3.7–3.1 (two qt, 2, CH_2CH_3), 1.2 (t, 3, CH_2CH_3, J = 8.0 Hz); M$^+$· 358 (62).

Anal. Calcd for $C_{18}H_{15}ClN_2SO_2$: C, 60.21; H, 4.21; N, 7.80. Found: C, 60.34; H, 4.08; N, 7.80.

General Procedure for Reaction of *N*-Benzoylsarcosine with Activated Isocyanates. Reaction with *p*-Toluenesulfonyl Isocyanate. *N*-Benzoylsarcosine[22] (1.93 g, 0.01 mol) in acetic anhydride (30 ml) at 40 °C was stirred and *p*-toluenesulfonyl isocyanate (1.97 g, 0.01 mol) added in small portions. Within 5 min a light yellow product had separated. Recrystallization from 1,2-dichloroethane afforded 7-methyl-1-phenyl-6-*p*-toluenesulfonyl-6,7-diaza-2-oxabicyclo[2.2.1]heptane-3,5-dione (**11**, R = *p*-

$CH_3C_6H_4SO_2$) as colorless prisms, 1.0 g (68%), mp 189–192 °C dec (with gas evolution).

Hydrolysis of 11 (R = *p*-$CH_3C_6H_4SO_2$). A. With Methanol. The adduct (0.7 g, 0.0019 mol) was refluxed in dry methanol for 4 h. Solvent was removed in vacuo and the residue recrystallized from ethanol, affording 2-methoxycarbonyl-2-(*N*-benzoyl-*N*-methylamino)acet-*p*-toluenesulfonamide (**12**) as small, colorless, clustered needles: 0.55 g (57%); mp 157–159 °C; ir (KBr) 3000 (broad, CH), 1750, 1720 cm^{-1} (CO); λ_{max} (CH_3OH) 226 nm (log ϵ 4.45); NMR ($CDCl_3$) δ 10.93 (bs, 1, NH, exchanged with D_2O), 7.17–7.97 (m, 9, aromatic), 5.33 (s, 1, C_2 H, exchanged with D_2O), 3.73 (s, 3, OCH_3), 3.00 (s, 3, NCH_3), 2.42 (s, 3, aryl CH_3); M^+· 403 (2).

Anal. Calcd for $C_{19}H_{20}N_2O_6S$: C, 56.56; H, 4.75; N, 6.95. Found: C, 56.45; H, 4.73; N, 6.83.

B. With 10% Sodium Hydroxide Solution. The adduct (1.0 g, 0.0027 mol) was heated on a steam bath with 10% sodium hydroxide (15 ml) for 5 min. The reaction mixture was cooled, neutralized with 3 N HCl, and extracted with chloroform. The chloroform layer was separated, dried over sodium sulfate, and evaporated in vacuo, leaving a colorless, crystalline residue which recrystallized from 1,2-dichloroethane–anhydrous ether yielding 2-(*N*-benzoyl-*N*-methylamino)acet-*p*-toluenesulfonamide (**13**) as colorless prisms: 0.2 g (20%); mp 156–157°; ir (KBr) 3000 (broad), 1710, 1625 cm^{-1}; λ_{max} (CH_3OH) 226 nm (log ϵ 4.32); NMR ($CDCl_3$) δ 7.17–7.92 (m, 9, aromatic), 4.13 (bs, 2, CH_2), 3.02 (s, 3, NCH_3), 2.43 (s, 3, aryl CH_3); M^+· 346 (6).

Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09. Found: C, 58.86; H, 5.13; N, 8.25.

Hydrolysis of 12. Treatment of **12** with 10% sodium hydroxide on a steam bath for 15 min, extraction of the reaction with chloroform, and evaporation of the chloroform extract afforded a colorless, crystalline solid identical[23] with **13** above.

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Registry No.—**1** (R = Ph), 13288-67-0; **1** (R = *p*-ClC_6H_4), 52730-97-9; **6**, 57513-31-2; **7**, 57513-32-3; **8**, 57513-33-4; **9**, 2568-34-5; **12**, 57513-34-5; **13**, 57513-35-6; phenyl isothiocyanate, 103-72-0; phenyl isocyanate, 103-71-9; benzoyl isocyanate, 4461-33-0; *p*-chlorobenzoyl isocyanate, 4461-36-3; trichloroacetyl isocyanate, 3019-71-4; *p*-toluenesulfonyl isocyanate, 4083-64-1; *N*-chlorosulfonyl isocyanate, 1189-71-5; acetyl isothiocyanate, 13250-46-9.

References and Notes

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Mesoionic Compounds. XXXVI. Reaction of Mesoionic Systems with Diphenylcyclopropene Derivatives[1]

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anhydro-2,3-Diphenyl-4-hydroxythiazolium hydroxide and diphenylcyclopropenone at 80° gave a 1:1 cycloadduct shown to be 2,3,5,6-tetraphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4,7-dione which, on thermolysis, lost the elements of COS forming 1,4,5,6-tetraphenyl-2(1*H*)-pyridone. With diphenylcyclopropenethione at room temperature the corresponding 7-oxo-2,3,5,6-tetraphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4-thione was formed which, on thermolysis, gave 3,4,6-triphenyl-2*H*-thiopyran-2-thione and 4-oxo-2,3,6,7-tetraphenyl-2*H*-1,3-thiazocinium 8-thiolate. *anhydro*-2-*p*-Chlorophenyl-4-hydroxy-3-phenylthiazolium hydroxide gave an analogous series of *p*-chlorophenyl substituted products. *anhydro*-2,4-Diphenyl-5-hydroxy-3-methyl-1,3-oxazolium hydroxide, generated in situ from *N*-benzoyl-*N*-methyl-*C*-phenylglycine and Ac_2O, and diphenylcyclopropenone gave 1-methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridone, and the corresponding thione was formed with diphenylcyclopropenethione. Reaction with 1,2,3-triphenylcyclopropene gave 1-methyl-2,3,4,5,6-pentaphenyl-1,4-dihydropyridine. *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium hydroxide and diphenylcyclopropenethione underwent reaction at room temperature giving 1-methyl-2,3,5-triphenyl-4(1*H*)-pyridinethione, whereas with diphenylcyclopropenone no reaction occurred. Chemical and spectral evidence used to establish these structures is described.

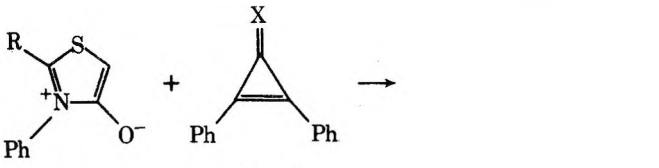
In the short time since the initial synthesis[2] of diphenylcyclopropenone, it has found applications as a versatile intermediate in organic synthesis.[3] As would be anticipated from its physical characteristics, it is a particularly interesting substrate in cycloaddition reactions and this property is shared to some degree by its thio analogue. Cycloadducts have been formed with carbonyl ylides,[4] heteroaromatic ring systems such as pyridine, pyridazine, etc.,[5] some 1,3-dipolar systems,[6] and also with enamines and other electron-rich olefinic systems.[7] Recently 1-azirines were

shown to react with diphenylcyclopropenone forming 4-pyridones.[8]

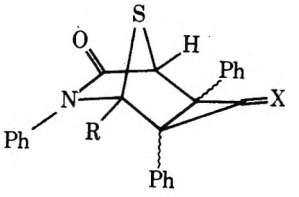
Previous papers in this series on mesoionic compounds described the reactions of the *anhydro*-2,3-disubstituted 4-hydroxythiazolium hydroxide system with acetylenic[9] and olefinic[10] dipolarophiles and, as a part of the study of the chemistry of mesoionic compounds,[11] we have investigated the reaction of this and several other mesoionic rings systems with diphenylcyclopropene derivatives.

anhydro-2,3-Diphenyl-4-hydroxythiazolium hydroxide (1, R = Ph) contains a "masked" thiocarbonyl ylide 1,3-dipole. Annelation of the three-carbon system of cyclopropene to the mesoionic ring offers the opportunity for a [3 + 3] cycloaddition with possible thermal ring expansions to six-membered and larger ring systems. Reaction of diphenylcyclopropenone with 1,3-dipoles has been observed to occur in three ways: addition across the carbonyl group;[6,12] addition across the carbon–carbon double bond;[13] a C–C insertion reaction such that the final product is an α,β-unsaturated ketone.[2c,4,7] The first two addition modes are usually accompanied by further skeletal rearrangement and, in the last, the initial reaction probably occurs at the C-2 atom of the three-membered ring.

Reaction of the mesoionic system 1 (R = Ph) and diphenylcyclopropenone in refluxing benzene gave a stable 1:1 adduct. Its molecular formula, $C_{30}H_{21}NO_2S$, established by analytical and mass spectral data, may be accommodated by structures **2**, **3**, **4**, or **5** (R = Ph; X = O), repre-



1 X = O,S



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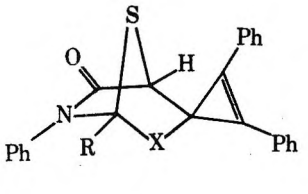

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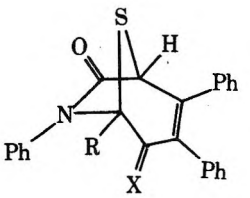

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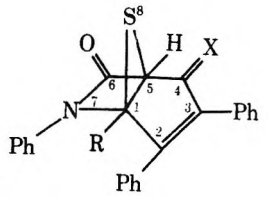

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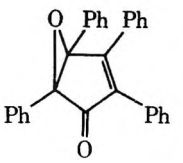


6

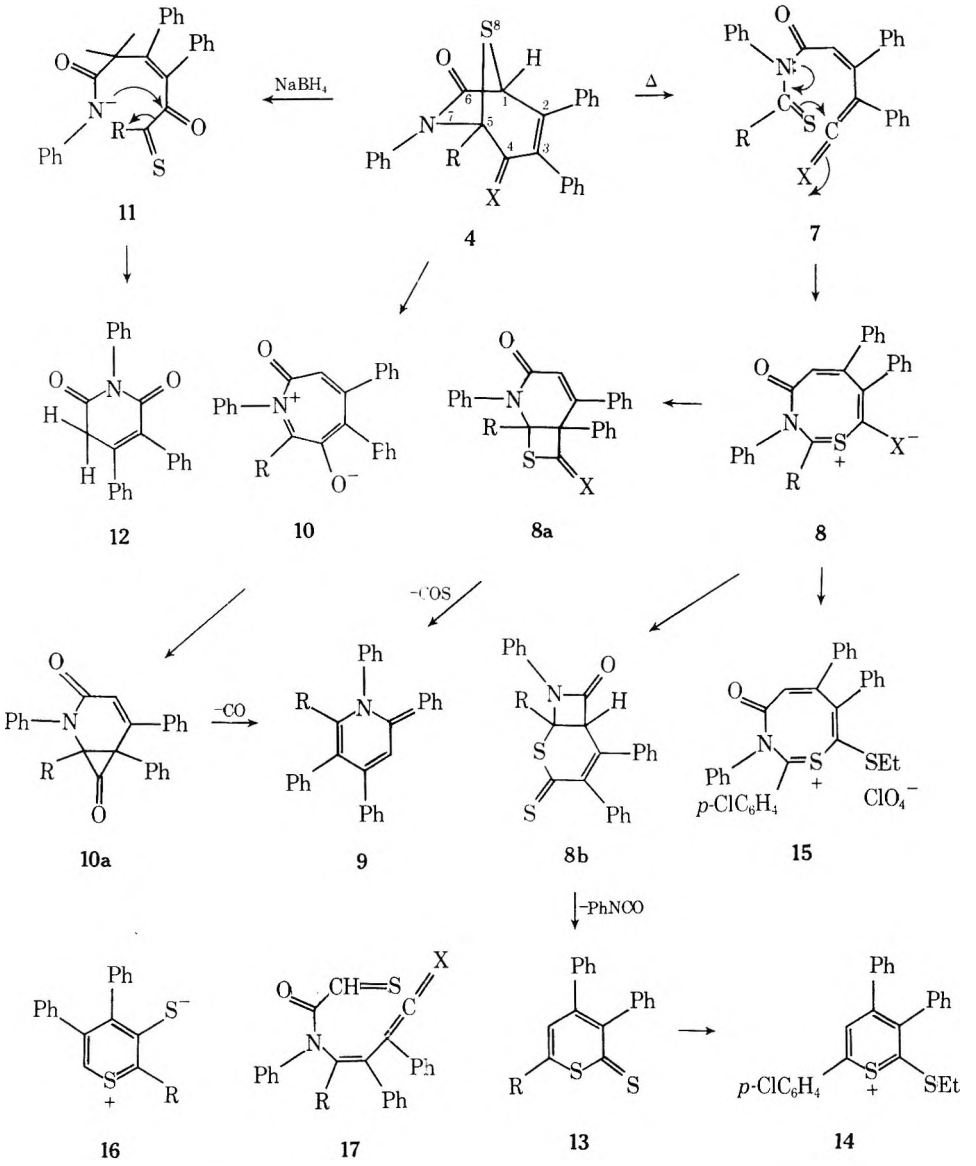
senting 1:1 adducts formed by the various addition modes described above. Structures **2** and **3** may be excluded immediately on the basis of the infrared spectral data. A carbonyl absorption at 1650 cm^{-1} attributed to the amide carbonyl group and an additional absorption at 1725 cm^{-1} are not consistent with a carbonyl group in a cyclopropane ring (for structure **2**, ν_{CO} ca. 1875–1800 cm^{-1})[14] nor with structure **3**. Structures **4** and **5** are, however, compatible with the additional carbonyl absorption at 1725 cm^{-1}, an analogous chromophore absorbing[15] at 1727 cm^{-1} in 4,5-epoxy-2,3,4,5-tetraphenylcyclopenten-1-one (**6**) and in 2,3-diphenylcyclopenten-2-one at 1681 cm^{-1}. This same chromophore in **6** has an ultraviolet absorption at 233 nm (log ϵ 4.23) and 338 (3.85), whereas the cycloadduct above exhibits its absorption maxima at 205 nm (log ϵ 4.64), 246 (4.45), 300 (4.26), and 353 (4.17). This shift to longer wavelength may be attributed to interaction of the bridge sulfur atom with the carbonyl chromophores of the amide and α,β-unsaturated ketone systems, a feature observed previously with adducts from **1** and heterocumulenes.[16]

A distinction between structures **4** and **5** can be made, however, on the basis of NMR data. In addition to the aromatic multiplet at δ 7.8–6.7 a singlet proton resonance was observed at δ 6.1 and this proton was not exchanged with D_2O–NaOD. This is more consistent with structure **4** than **5**, for in the latter this bridgehead proton would be expected to be at much lower field, being in the deshielding zones of the two flanking carbonyl groups. Though there is a change in the geometry of the bicyclo[3.2.1]octane system compared to the bicyclo[2.2.1]heptane system present in the cycloadducts from **1** and heterocumulenes,[16] it should not be sufficient to result in a chemical shift change from ca. δ 10 to δ 6.1.

The mass spectrum of **4** (R = Ph; X = O) is particularly informative. A fragmentation of the molecular ion, *m/e* 459.1291, involves the loss of CO giving an ion $C_{29}H_{21}NOS$ (*m/e* 431.1396) corresponding to the product anticipated from the reaction of **1** (R = Ph) and diphenylacetylene. The cycloreversion of this process was observed with the formation of the diphenylacetylene ion $C_{14}H_{10}$ (*m/e* 178.0803) and the ion corresponding to **1** (R = Ph), $C_{15}H_{11}NOS$ (*m/e* 253.0580).[17] These processes can only be interpreted in terms of structures **4** or **5**. Additional evidence in support of **4** comes from the formation of 1,4,5,6-tetraphenyl-2(1*H*)-pyridone (**9**, R = Ph) on thermolysis of **4** (R = Ph; X = O). Cleavage of the 4,5 bond in **4** to the intermediate ketene **7** (R = Ph; X = O), followed by rearrangement through the resonance-stabilized betaine **8** (R = Ph; X = O) and its valence tautomer **8a** (R = Ph; X = O), provides a satisfactory explanation for the formation of **9** (R = Ph). An alternative route, initiated by loss of S from **4** to give an intermediate betaine **10** (R = Ph) followed by rearrangement to **10a** (R = Ph) with subsequent loss of CO, is relatively unlikely. Experience has shown that loss of S from adducts such as **4** only occurs readily when an aromatic ring system is formed in the process.[10,16] This thermal rearrangement dictates against the alternative formulation of the adduct as structure **5**. Although cleavage of the 4,5 bond in **5** would give rise to a ketene intermediate **17** (X = O) that, by ring closure and elimination of COS as above, would give the pyridone **9**, the intermediate **17** would be anticipated to be an extremely unstable product with little tendency to undergo ring closure to an intermediate analogous to **8** (X = O).

The structure of the pyridone **9** was assigned on the basis of analytical and spectral data. Mass spectrometry and analytical data established the molecular formula as $C_{29}H_{21}NO$ and, in addition to the aromatic proton multiplet at δ 7.1–7.8 in the NMR spectrum, a sharp singlet occurred at δ 6.4. The analogous 3 proton in 2-pyridone has been observed[18] at δ 6.57, substituents in the ring having only minor effects on this chemical shift.

Reaction of *anhydro*-2-*p*-chlorophenyl-4-hydroxy-3-phenylthiazolium hydroxide (1, R = *p*-ClC_6H_4) with diphenylcyclopropenone gave rise to the 5-*p*-chlorophenyl



analogue of **4** (R = p-ClC_6H_4) with spectral characteristics consistent with those of **4** (R = Ph).

The action of $NaBH_4$ on **4** (R = Ph or p-ClC_6H_4; X = O) gave a product of molecular formula $C_{23}H_{17}NO_2$, requiring loss of the C_5 atom as some combination of RCS. The isolation of a small amount of sulfur-containing polymeric substance indicates that this species was most likely the appropriate thioaldehyde. Structure **12** readily accommodates two carbonyl groups at 1740 and 1670 cm^{-1}, and may be formed by hydride ion attack at the C_1 bridgehead position in preference to the more sterically hindered C_5 position with formation of **11**, followed by ring closure to **12**. In agreement with this structure, the NMR spectrum of **12**, 1,3,4-triphenyl-2,6-dioxo-1,2,5,6-tetrahydropyridine, showed a two-proton singlet at δ 4.00 in addition to the aromatic protons at δ 6.87–7.60.

Diphenylcyclopropenethione also reacted readily with **1** forming 1:1 cycloadducts at room temperature in anhydrous benzene over 18 h, these adducts being assigned the structure of 7-oxo-2,3,5,6-tetraphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4-thione (**4**, R = Ph; X = S). The chemical shift of the C_1 bridgehead proton was observed at δ 6.2, a chemical shift inconsistent with the alternative structure **5** (R = Ph; X = S) in which the bridgehead proton would be in the deshielding zone of both the C_7 carbonyl group and the C_2 thiocarbonyl group. Absorptions consistent with a C=S group were observed in the 1020–1250-cm^{-1} region and an absorption at 1650 cm^{-1} may be attributed to the C_7 carbonyl group.

On thermoylsis, **4** (R = Ph, p-ClC_6H_4; X = S) formed two brilliant-red products. The first product isolated from chromatography of the reaction mixture was identified as 6-aryl-3,4-diphenyl-2*H*-thiopyran-2-thione (**13**, R = Ph, p-ClC_6H_4). Its spectral characteristics, especially the NMR data and ultraviolet absorption, were consistent with data reported for analogous structures in the literature, and the 3,4,6-triphenyl derivative **13** (R = Ph) was synthesized by an alternative route utilizing the reaction of 1-(benzoylmethyl)pyridinium bromide and diphenylcyclopropenone[19] to give the 3,4,6-triphenyl-2*H*-pyran-2-one which was converted into the 2-thione with P_4S_{10}–pyridine, and the 2*H*-pyran-2-thione isomerized[20] to the corresponding 2*H*-thiopyran-2-one which finally with P_4S_{10}–pyridine gave the 2*H*-thiopyran-2-thione **13** (R = Ph). Reaction with Meerwein's reagent gave the corresponding 2-ethylthio derivative **14**.

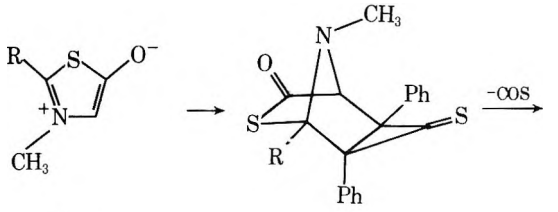
The second product formed in the thermolysis was isomeric with **4** (R = Ph, p-ClC_6H_4; X = S). Structure **8** (R = Ph, p-ClC_6H_4; X = S), 2-aryl-4-oxo-3,6,7-triphenyl-2*H*-1,3-thiazocinium 8-thiolate, was consistent with its chemical and spectral properties, and it reacted readily with Meerwein's reagent to give the corresponding SEt product **15**. The chemical shift of the methylene protons at δ 3.3 (qt) correlates well with an SEt group adjacent to a posi-

tively charged sulfur atom rather than with those of an OEt group.[21]

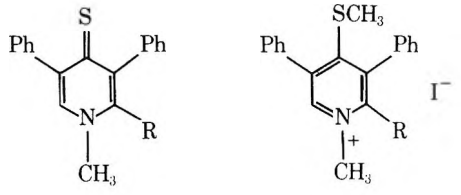
In the thermolysis of **4** (X = O, S), the intermediate ketene **7** (X = O) and thioketene **7** (X = S) satisfactorily explain all the observed products. Ring closure to **8** (X = O) ultimately leads[22] to the pyridone **9** whereas in **8** (X = S) an alternative valence isomerization to **8b** and subsequent loss of phenyl isocyanate give the thiopyranthione **13**. A product **16** isomeric with **13** could conceivably be derived by elimination of PhNCO from **4** (X = S) but, as shown above, this retrocycloaddition is not favored in this thermolysis over fission of the 4,5 bond. Similarly the intermediacy of the ketene **17** (X = O) or thioketene (X = S) derived from **5** can be excluded by the above results.

In contrast to the ready reaction of **1** with diphenylcyclopropenone and diphenylcyclopropenethione, the 5-phenyl derivative of **1** did not undergo any reaction, an observation also noted by others.[23]

The isomeric thiazole mesoionic system **18** and diphenylcyclopropenone in refluxing benzene did not form a cycloadduct. Instead the diphenylcyclopropenone dimer was isolated. In view of the reaction reported recently[23] for its 4-phenyl derivative, this failure to isolate a product is probably due to the thermal instability of **18**, a not uncommon occurrence in cycloadditions with this ring system. However, with diphenylcyclopropenethione, **18** (R = Ph, *p*-ClC_6H_4), readily gave a product in benzene at room temperature identified as 2-aryl-3,5-diphenyl-1-methyl-4(1*H*)-pyridinethione (**20**, R = Ph, *p*-ClC_6H_4). The most direct route to this product involves an intermediate such as **19** (see below) which loses COS to form the observed product.



18 **19**

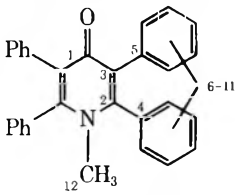


20 **21**

The following spectral data for **20** are consistent with a thiopyridone structure. In the infrared spectrum a C=C absorption at 1610 cm^{-1} and absorption maxima in its ultraviolet spectrum [360 nm (log ϵ 3.96), 267 (3.71), and 226 (4.13)] were analogous to those reported for the thiopyridone **24** (X = S). The C_6 H was masked in the aromatic multiplet between δ 7.00 and 8.00 in the NMR spectrum, and the mass spectrum gave a fragmentation pattern analogous to that obtained for **24** (X = S). When **20** was converted into a methylated derivative **21** with methyl iodide, the C_6 proton was shifted downfield to δ 8.74.

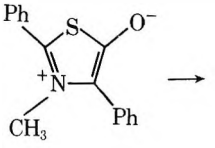
The different modes of cycloaddition of the isomeric thiazolium mesoionic systems suggested extension of these studies to other mesoionic systems. 3-Phenyl- and 3-methylsydnone were found to be unreactive with diphenylcyclopropenone and its thione but *anhydro*-2,4-diphenyl-5-hydroxy-3-methyl-1,3-oxazolium hydroxide (**22**) reacted readily. This mesoionic system can be utilized most effectively

Table I. ^{13}C Chemical Shifts of 1-Methyl-2,3,5,6-tetraphenyl-4-pyridone[25b]

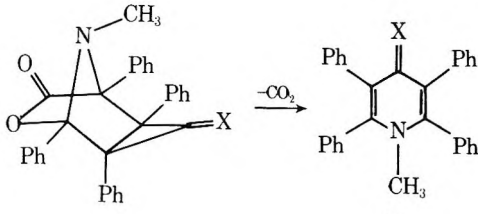


Assigned carbon	Chemical shift, ppm	Assigned carbon	Chemical shift, ppm
1	189.7	5	134.9
2	175.3	6–11	126.2–131.3
3	149.5	12	41.3
4	135.5		

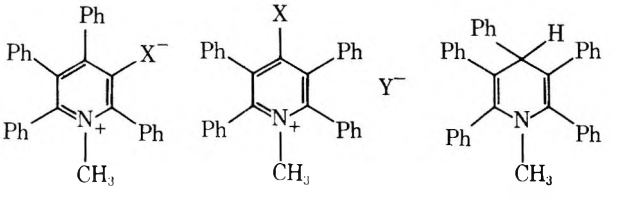
by generation *in situ* from *N*-benzoyl-*N*-methyl-*C*-phenylglycine and acetic anhydride[24] and when this mixture was heated at 85°C for 10 min with diphenylcyclopropenone, 1-methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridone (**24**, X = O) was obtained as colorless needles. The reaction may proceed through the intermediacy of a cyclopropanone **23** (X = O) with concomitant loss of CO_2 to the pyridone **24** (X = O). However, alternative modes of addition to **22** are possible, and would result in the formation of the isomer, *anhydro*-3-hydroxy-1-methyl-2,4,5,6-tetraphenylpyridinium hydroxide (**25**, X = O). Spectral data (Experimental Section), especially ν_{CO} 1620 cm^{-1}, do not allow an unambiguous assignment of structure but favor structure **24** over **25**.



22



23 **24**



25 **26** **27**

The simplicity of the ^{13}C PFT spectrum of the product is indicative of the symmetry within **24** which theoretically should give rise to a 12-line spectrum. Chemical shifts (downfield from Me_4Si) and carbon assignments are shown in Table I. The pyridone **24** (X = O) was characterized further by conversion with Meerwein's reagent into 4-ethoxy-1-methyl-2,3,5,6-tetraphenylpyridinium tetrafluoroborate (**26**, X = OEt; Y = BF_4) whose spectral data are fully consistent with this structural assignment. An interesting feature of the mass spectrum of the salt **26** (X = OEt; Y = BF_4) was the incorporation of fluorine into the pyridine ring. It may be speculated that, after initial, thermal loss of BF_3, the residual fluorine covalently bonds with the pyridine ring, most likely at the 2 position, and accounts for a

series of ions, $C_{32}H_{28}FNO$, *m/e* 461 (11), $C_{32}H_{29}FNO$, *m/e* 460 (5), and $C_{30}H_{23}FNO$, *m/e* 432 (2).

Confirmation of the structure of the product from **22** and diphenylcyclopropenone as **24** (X = O) was obtained by its synthesis by an alternative route from 2,3,5,6-tetraphenyl-4(4*H*)-pyrone and methylamine.[25a]

When diphenylcyclopropenethione and *N*-benzoyl-*N*-methyl-*C*-phenylglycine were heated in acetic anhydride at 40 °C for 5 min, a product crystallized from solution and corresponded to the loss of CO_2 from a primary cycloadduct. Ambiguity in structural assignment exists in this case as well, depending upon the mode of cycloaddition to **22.** If C=C addition to **22** had occurred, then 1-methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridinethione (**24,** X = S) would result. If C–CS insertion had occurred, then *anhydro*-3-mercapto-1-methyl-2,4,5,6-tetraphenylpyridinium hydroxide (**25,** X = S) would be formed. That C=C addition had occurred was demonstrated by the synthesis of **24** (X = S) from **24** (X = O) and P_4S_{10} in refluxing pyridine. This reaction, and that of **18** with diphenylcyclopropenethione, represent the first examples of addition to the C=C bond of diphenylcyclopropenethione, insertion between C_1–C_2 being the usual mode of reaction. The spectral data, consistent with this structure, are described in the Experimental Section. The thione was readily converted into the corresponding *S*-methyl product **26** (X = CH_3S; Y = I) with methyl iodide and alkylated with triethyloxonium tetrafluoroborate to 4-ethylthio-1-methyl-2,3,5,6-tetraphenylpyridinium tetrafluoroborate (**26,** X = EtS; Y = BF_4).[26]

1,2,3-Triphenylcyclopropene reacted in an analogous fashion with **22,** giving 1-methyl-2,3,4,5,6-pentaphenyl-1,4-dihydropyridine (**27**), this product being reported recently as having been prepared from an isolated sample of **22** and the cyclopropene.[27]

Experimental Section[28]

2,3,5,6-Tetraphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4,7-dione (4, R = Ph; X = O). *anhydro*-2,3-Diphenyl-4-hydroxythiazolium hydroxide (**1**, R = Ph) (5.0 g, 0.02 mol) and diphenylcyclopropenone (4.0 g, 0.02 mol) in dry benzene were refluxed for 30 min. The solvent was removed in vacuo and the residue chromatographed on Kieselgel G (benzene) using $CHCl_3$ as eluent. Crystallization from chloroform–cyclohexane afforded yellow needles of **4** (R = Ph; X = O): 2.0 g (27%); mp 198–200 °C; ir (KBr) 1725, 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 353 nm (log ϵ 4.17), 300 (4.26), 246 (4.45); NMR ($CDCl_3$) δ 6.71–7.83 (m, 20, aromatic), 6.10 (s, 1, C_4 H); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 459.1291 (0.34), $[M - CO]^{\cdot+}$ 431.1396 (2).

Anal. Calcd for $C_{30}H_{21}NO_2S$: C, 78.41; H, 4.61; N, 3.05. Found: C, 78.49; H, 4.66; N, 2.94.

5-*p*-Chlorophenyl-2,3,6-triphenyl-6-aza-8-thiabicyclo-[3.2.1]oct-2-ene-4,7-dione (4, R = *p*-ClC_6H_4; X = O) was prepared from **1** (R = *p*-ClC_6H_4) in a similar manner. It crystallized from benzene–anhydrous ether as yellow needles: mp 137–139 °C dec; ir (KBr) 1720, 1660 cm^{-1} (CO); NMR ($CDCl_3$) δ 6.70–7.62 (m, 19, aromatic), 6.10 (s, 1, C_4 H).

Anal. Calcd for $C_{30}H_{20}ClNO_2S$: C, 72.94; H, 4.05; N, 2.84. Found: C, 72.59; H, 4.62; N, 2.71.

Thermolysis of 2,3,5,6-Tetraphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4,7-dione (4, R = Ph; X = O). The above cycloadduct (500 mg) was heated at 200 °C (1 mm) for 20 min. After melting and gas evolution (~15 min) the oil solidified. This product was chromatographed on Kieselgel G (benzene) using chloroform as eluent. 1,4,5,6-Tetraphenyl-2(1*H*)-pyridone (**9**, R = Ph) crystallized from chloroform–ether as colorless needles: 350 mg (80%); mp 279–281 °C; ir (KBr) 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 340 nm (log ϵ 4.05), 243 (4.28); NMR ($CDCl_3$) δ 7.14–7.81 (m, 2, aromatic), 6.40 (s, 1, C_3 H); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 399 (100).

Anal. Calcd for $C_{29}H_{21}NO$: C, 87.19; H, 5.30; N, 3.51. Found: C, 86.57; H, 5.26; N, 3.27.

Sodium Borohydride Reduction of 4 (R = Ph; X = O). The cycloadduct **4** (R = Ph; X = O) (500 mg) in ethanol (100 ml) was treated with a solution of $NaBH_4$ (120 mg) in ethanol (20 ml). After 4 h at room temperature, the solvent was removed, water added, and the aqueous solution extracted with $CHCl_3$ (2 × 50 ml). After drying (Na_2SO_4) the chloroform extract was evaporated to dryness and the residue chromatographed on Kieselgel G (benzene) using $CHCl_3$ as eluent. The product **12** crystallized from chloroform–petroleum ether or benzene–petroleum ether (bp 35–60 °C) as colorless needles: 250 mg, mp 228–230 °C; ir (KBr) 3050 (CH), 1740, 1670 cm^{-1} (CO); λ_{max} (CH_3OH) 356 nm (log ϵ 4.07), 246 sh (4.19); NMR ($CDCl_3$) δ 6.87–7.60 (m, 15, aromatic), 4.00 (s, 2, CH_2); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 339.1284 (44), $[M - PhNCO]^{\cdot+}$ 220.0889 (100).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.55; H, 5.13; N, 3.88.

5-*p*-Chlorophenyl-2,3,6-triphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4,7-dione (**4**, R = *p*-ClC_6H_4; X = O) was treated with $NaBH_4$ as above. The product isolated was identical[29] with **14.**

Reaction of *anhydro*-2-Aryl-4-hydroxy-3-phenylthiazolium Hydroxide (1) with Diphenylcyclopropenethione. The mesoionic compound **1** (R = *p*-ClC_6H_4) (2.8 g, 0.01 mol) and diphenylcyclopropenethione (2.2 g, 0.01 mol) were stirred in dry benzene (200 ml) for 18 h. The solvent was removed in vacuo, and the residue chromatographed on silica gel (chloroform). The first band was collected, solvent removed in vacuo, and the red, oily residue dissolved in anhydrous ether, from which orange needles of 5-*p*-chlorophenyl-7-oxo-2,3,6-triphenyl-6-aza-8-thiabicyclo[3.2.1]oct-2-ene-4-thione (**4**, R = *p*-ClC_6H_4; X = S) separated on standing overnight: 2.5 g (43%); mp 163–165 °C dec; ir (KBr) 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 427 nm (log ϵ 4.05), 294 (4.43), 237 sh (4.41); NMR ($CDCl_3$) δ 6.83–7.66 (m, 19, aromatic), 6.23 (s, 1, C_4 H).

Anal. Calcd for $C_{30}H_{20}ClNOS_2$: C, 70.64; H, 3.95; N, 2.75. Found: C, 70.79; H, 4.01; N, 2.75.

Similarly, 7-oxo-2,3,5,6-tetraphenyl-6-aza-8-thiabicyclo[3.2.1]-oct-2-ene-4-thione (**4**, R = Ph; X = S) crystallized from benzene–petroleum ether (bp 60–80°) as orange prisms: 30%, mp 170–172 °C; ir (KBr) 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 425 nm (log ϵ 4.01), 293 (4.38), 239 (4.32); NMR ($CDCl_3$) δ 7.8–6.7 (m, 20, aromatic), 6.29 (s, 1, C_4 H); mass spectrum *m/e* $M^{\cdot+}$ 475.1063, $[M - PhNCO]^{\cdot+}$ 356.0643.

Anal. Calcd for $C_{30}H_{21}NOS_2$: C, 75.78; H, 4.45; N, 2.95. Found: C, 75.69; H, 4.38; N, 2.88.

Thermolysis of 4 (R = *p*-ClC_6H_4; X = S). The 1:1 adduct **4** (R = *p*-ClC_6H_4; X = S) (1.0 g, 0.002 mol) was heated under vacuum (ca. 25 mm) to 170 °C and left at that temperature for 10 min until the gas evolution subsided. The dark residue was chromatographed on silica gel (benzene). The first dark band was collected, the solvent removed in vacuo, and the dark-red residue recrystallized from ethanol forming a three-component product. This product was chromatographed on preparative silica gel (chloroform), the first band isolated, and recrystallized from ethanol yielding deep-red, irregular prisms of 6-*p*-chlorophenyl-3,4-diphenyl-2*H*-thiopyran-2-thione (**13,** R = *p*-ClC_6H_4): 150 mg (21%); mp 148–155 °C dec; ir (KBr) 3050 cm^{-1} (CH); λ_{max} (CH_3OH) 477 nm (log ϵ 3.90), 338 sh (4.07), 312 (4.23), 250 (4.45); NMR ($CDCl_3$) δ 7.00–7.66 (m, aromatic).

Anal. Calcd for $C_{23}H_{15}ClS_2$: C, 70.66; H, 3.87. Found: C, 70.77; H, 3.87.

The second dark band was collected, solvent removed in vacuo, and the residue recrystallized from benzene yielding 2-*p*-chlorophenyl-4-oxo-3,6,7-triphenyl-3*H*-1,3-thiazocinium 8-thiolate (**8**, R = *p*-ClC_6H_4) as dark brown needles: 300 mg (30%); mp 249–251 °C; ir (KBr) 3080 (CH), 1670 (CO), 1630 cm^{-1} (C=N); λ_{max} (CH_3OH) 460 nm (log ϵ 3.68), 328 (3.95), 244 (4.39); NMR ($CDCl_3$) δ 6.50–7.46 (m, aromatic); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 509 (25).

Anal. Calcd for $C_{30}H_{20}ClNOS_2$: C, 70.64; H, 3.95; N, 2.75. Found: C, 70.58; H, 3.87; N, 2.59.

Similarly, thermolysis of **4** (R = Ph; X = S) gave 3,4,6-triphenyl-2*H*-thiopyran-2-thione (**13,** R = Ph) as deep maroon needles from benzene–petroleum ether: 27%; mp 160–162 °C; ir (KBr) 1560, 1460, 1205, 752, 695 cm^{-1}; λ_{max} (CH_3OH) 480 nm (log ϵ 4.14), 330 sh (4.30), 308 (4.44), 245 (4.63); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 356 (70), $[M - 1]^+$ 355 (100).

Anal. Calcd for $C_{23}H_{16}S_2$: C, 77.49; H, 4.52. Found: C, 77.83; H, 4.53.

The second product from this thermolysis, 4-oxo-2,3,6,7-tetraphenyl-3*H*-1,3-thiazocinium 8-thiolate (**8**, R = Ph), was likewise obtained as deep maroon prisms: 20%; mp 248–250 °C; ir (KBr)

1650, 1600, 1540, 1440, 1050, 750, 685 cm^{-1}; λ_{max} (CH_3OH) 463 nm (log ϵ 3.88), 328 (4.11), 240 (4.56); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 475 (100), $[M-1]^+$ 474 (63), $[M-93]^+$ 382 (89).

Anal. Calcd for $C_{30}H_{21}NOS_2$: C, 75.75; H, 4.45; N, 2.95. Found: C, 75.34; H, 4.31; N, 2.81.

Reaction of 6-*p*-Chlorophenyl-3,4-diphenyl-2*H*-thiopyran-2-thione (13, R = *p*-ClC_6H_4) with Triethyloxonium Tetrafluoroborate. The above thione (0.3 g, 0.0008 mol) in dry methylene chloride (20 ml) was treated with an excess of triethyloxonium tetrafluoroborate added in small portions at room temperature. After 5 days anhydrous Et_2O was added causing an orange solid to separate. Recrystallization from ethanol afforded 6-*p*-chlorophenyl-3,4-diphenyl-2-ethylthio-2*H*-thiopyrylium tetrafluoroborate (**14**) as rust-colored plates: 0.25 g (27%); mp 204–207 °C dec; ir (KBr) 1350, 1050 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 436 nm (log ϵ 4.04), 304 (4.06), 253 (4.29); NMR ($CDCl_3$) δ 8.17 (s, 1, C_6 H), 7.73 (A_2B_2 qt, 4, *p*-ClC_6H_4), 7.30 (bs, 10, aromatic), 3.45 (qt, 2, SCH_2CH_3), 1.47 (t, 3, SCH_2CH_3).

Anal. Calcd for $C_{25}H_{20}BClF_4S_2$: C, 59.24; H, 3.98. Found: C, 59.07; H, 3.93.

Reaction of 2-*p*-Chlorophenyl-4-oxo-3,6,7-triphenyl-3*H*-1,3-thiazocinium 8-Thiolate (8, R = *p*-ClC_6H_4) with Triethyloxonium Tetrafluoroborate. The thiolate (0.25 g, 0.005 mol) in dry methylene chloride (40 ml) was treated with triethyloxonium tetrafluoroborate (0.4 g, 0.002 mol) added in small portions with an immediate lightening in color of the reaction mixture. Stirring was continued for 30 min, anhydrous ether (100 ml) added, and excess triethyloxonium tetrafluoroborate filtered off. Evaporation of the solvent left a yellow oil that was dissolved in EtOH (10 ml) and treated with perchloric acid (20 ml, 70%). The resultant yellow solid crystallized from ethanol, giving 2-*p*-chlorophenyl-8-ethylthio-4-oxo-3,6,7-triphenyl-3*H*-1,3-thiazocinium perchlorate (**15**) as yellow-orange prisms: 0.7 g (74%); mp 160–165 °C dec; ir (KBr) 1690 cm^{-1} (C=N^+–); λ_{max} (CH_3OH) 428 nm (log ϵ 3.63), 305 sh (3.64), 244 (4.14); NMR ($CDCl_3$) δ 9.05 (s, 1, C_5 H), 7.00–8.06 (m, 19, aromatic), 3.37 (qt, 2, OCH_2CH_3), 1.55 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{32}H_{25}Cl_2NO_5S_2$: C, 60.18; H, 3.95; N, 2.19. Found: C, 60.33; H, 3.95; N, 2.19.

Reaction of *anhydro*-5-Hydroxy-3-methyl-2-phenylthiazolium Hydroxide (18) with Diphenylcyclopropenethione. At room temperature, a mixture of the mesoionic compound 18 (R = Ph) (1.2 g, 0.005 mol), diphenylcyclopropenethione (1.4 g, 0.005 mol), and dry benzene (25 ml) was stirred for 12 h. Filtration of the precipitated solid, chromatography on preparative silica gel (ethyl acetate), and crystallization from chloroform–petroleum ether (bp 60–90 °C) gave 1-methyl-2,3,5-triphenyl-4(1*H*)-pyridinethione (**20**, R = Ph) as yellow needles: 450 mg (20%); mp 240–245 °C dec; ir (KBr) 3030 (CH), 1610 cm^{-1} (C=C); λ_{max} (CH_3OH) 360 nm (log ϵ 3.96), 267 (3.71), 226 (4.13); NMR ($CDCl_3$) δ 7.00–8.00 (m, 16, aromatic and C_6 H), 3.40 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 353 (58), 352 (100), M^{2+} 176.5 (5).

Anal. Calcd for $C_{24}H_{19}NS$: N, 3.96. Found: N, 4.01.

It was characterized further by reaction with methyl iodide in methanol at room temperature for 6 h. Concentration of solvent under reduced pressure and addition of anhydrous ether precipitated a yellow solid which was filtered, washed with several portions of anhydrous ether, and recrystallized from ethanol–anhydrous ether affording yellow needles of 4-methylthio-1-methyl-2,3,5-triphenylpyridinium iodide (**21**, R = Ph): 72%; mp 207–210 °C dec; ir (KBr) 3060 (CH), 1610 cm^{-1} (C=N); λ_{max} (CH_3OH) 325 nm (log ϵ 3.56), 271 (3.77), 219 sh (4.05); NMR ($CDCl_3$) δ 8.74 (s, 1, C_6 H), 7.10–7.92 (m, 15, aromatic), 4.04 (s, 3, NCH_3), 1.72 (s, 3, SCH_3).

Anal. Calcd for $C_{25}H_{22}INS$: C, 60.61; H, 4.48; N, 2.83. Found: C, 60.87; H, 4.45; N, 2.92.

Similarly, reaction of *anhydro*-2-*p*-chlorophenyl-5-hydroxy-3-methylthiazolium hydroxide (18, R = *p*-ClC_6H_4) and diphenylcyclopropenethione afforded 2-*p*-chlorophenyl-3,5-diphenyl-1-methyl-4(1*H*)-pyridinethione (**20**, R = *p*-ClC_6H_4) as yellow needles: 34%; mp 265–268 °C dec; ir (KBr) 3050 (CH), 1630 cm^{-1} (C=N); λ_{max} (CH_3OH) 359 nm (log ϵ 4.01), 287 (3.95), 247 (4.27); NMR ($CDCl_3$) δ 7.00–7.71 (m, 15, aromatic and C_6 H), 3.38 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 387 (74), 386 (100), M^{2+} 193.5 (2).

Anal. Calcd for $C_{24}H_{18}ClNS$: N, 3.61. Found: N, 3.32.

It was characterized as above by conversion into 2-*p*-chlorophenyl-3,5-diphenyl-4-methylthio-1-methylpyridinium iodide (**21**, R = *p*-ClC_6H_4) obtained as yellow, irregular prisms from ethanol–anhydrous ether: 65%; mp 204–207 °C dec; ir (KBr) 1610 cm^{-1} (C=N); λ_{max} (CH_3OH) 325 nm (log ϵ 4.09), 272 (4.16), 218 sh (4.57); NMR ($CDCl_3$) δ 8.73 (s, 1, C_6 H), 7.17–8.00 (m, 14, aromatic), 4.03 (s, 3, NCH_3), 1.75 (s, 3, SCH_3).

Anal. Calcd for $C_{25}H_{21}ClINS$: C, 56.66; H, 4.00; N, 2.64. Found: C, 56.52; H, 3.87; N, 2.61.

Alkylation of 2-*p*-Chlorophenyl-3,5-diphenyl-1-methyl-4-pyridinethione (20, R = *p*-ClC_6H_4) with Triethyloxonium Tetrafluoroborate. The title compound (0.6 g, 0.0016 mol) in methylene chloride (25 ml) was treated with an excess of triethyloxonium tetrafluoroborate, and the reaction mixture stirred at room temperature for 24 h. Addition of excess anhydrous ether, filtration, and recrystallization from ethanol gave 2-*p*-chlorophenyl-3,5-diphenyl-4-ethylthio-1-methylpyridinium tetrafluoroborate as yellow needles: 0.8 g (100%); mp 198–200 °C dec; ir (KBr) 3050, 2975, 2940 (CH), 1620 cm^{-1} (CN); λ_{max} (CH_3OH) 326 nm (log ϵ 3.96), 276 (4.08), 237 sh (4.25); NMR ($CDCl_3$) δ 8.23 (s, 1, C_6 H), 6.97–7.90 (m, 14, aromatic), 3.90 (s, 3, NCH_3), 2.07 (qt, 2, CH_2CH_3), 0.85 (t, 3, CH_2CH_3).

Anal. Calcd for $C_{26}H_{23}BClF_4NS$: C, 61.98; H, 4.60; N, 2.78. Found: C, 62.10; H, 4.62; N, 2.81.

Reaction of *anhydro*-2,4-Diphenyl-5-hydroxy-3-methyloxazolium Hydroxide (22) with Diphenylcyclopropenone. *N*-Benzoyl-*N*-methyl-*C*-phenylglycine (3.6 g, 0.013 mol), diphenylcyclopropenone (2.4 g, 0.012 mol), and acetic anhydride (50 ml) were stirred and heated to 85 °C. After 10 min a colorless solid separated and heating was discontinued. Recrystallization from chloroform–anhydrous ether gave 1-methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridone (**24**, X = O) as colorless needles: 1.4 g (29%); mp 309–310 °C (lit.[25a] mp 309–310 °C, sealed tube 317–318 °C); ir (KBr) 3050 (CH), 1620 cm^{-1} (CO); λ_{max} (CH_3OH) 276 nm (log ϵ 4.12), 236 sh (4.36); NMR ($CDCl_3$) δ 7.23 (s, 10, aromatic), 7.07 (s, 10, aromatic), 3.03 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 413 (58), $[M-1]^+$ 412 (100), M^{2+} 206.5 (5).

Anal. Calcd for $C_{30}H_{23}NO$: C, 87.14; H, 5.60; N, 3.39. Found: C, 87.07; H, 5.56; N, 3.26.

Alkylation of 24 (X = O) with Triethyloxonium Tetrafluoroborate. The pyridone (0.5 g, 0.0012 mol) in methylene chloride (25 ml) was treated with an excess of triethyloxonium tetrafluoroborate and stirred at room temperature for 48 h. Anhydrous ether was added and the resultant precipitate recrystallized from ethanol, forming colorless needles of 4-ethoxy-1-methyl-2,3,5,6-tetraphenylpyridinium tetrafluoroborate (**26**, X = OEt; Y = BF_4): 0.65 g (100%); mp 275–278 °C dec; ir (KBr) 3050, 2980 (CH), 1610 cm^{-1} (C=N); λ_{max} (CH_3OH) 290 sh nm (log ϵ 3.94), 243 (4.41); NMR ($CDCl_3$) δ 7.00–7.73 (m, 20, aromatic), 3.63 (s, 3, NCH_3), 3.55 (qt, 2, CH_2CH_3), 0.67 (t, 3, CH_2CH_3); mass spectrum *m/e* (rel intensity) 412 (100).

Anal. Calcd for $C_{32}H_{28}BF_4NO$: C, 72.60; H, 5.33; N, 2.65. Found: C, 72.51; H, 5.35; N, 2.53.

Formation of 1-Methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridinethione (24, X = S). *N*-Benzoyl-*N*-methyl-*C*-phenylglycine (1.5 g, 0.0056 mol) was dissolved in acetic anhydride (20 ml) and to this solution at 40 °C was added diphenylcyclopropenethione (1.24 g, 0.0056 mol). Within 5 min an orange solid had precipitated and was filtered after stirring for 2 h. Recrystallization from chloroform–anhydrous ether afforded **24** (X = S) as yellow-orange, irregular prisms: 2.9 g (68%); mp 320–322° dec; ir (KBr) 3040 (CH), 1605 cm^{-1} (C=N); λ_{max} (CH_3OH) 360 nm (log ϵ 4.18), 272 sh (3.80), 238 (4.18); NMR ($CDCl_3$) δ 7.10, 7.23, 7.27 (3, s, 20, aromatic), 3.05 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 429 (60), $[M-1]^+$ 428 (100), M^{2+} 214.5 (5).

Anal. Calcd for $C_{30}H_{23}NS$: C, 83.88; H, 5.40; N, 3.26. Found: C, 83.89; H, 5.29; N, 3.07.

Treatment of 1-methyl-2,3,5,6-tetraphenyl-4(1*H*)-pyridone (**24**, X = O) with a 1.5-fold excess of P_4S_{10} in refluxing pyridine afforded, after preparative thin layer chromatography, a product identical[29] with 1-methyl-2,3,4,5-tetraphenyl-4(1*H*)-pyridinethione (**24**, X = S) obtained above.

Alkylation of 24 (X = S) with Methyl Iodide. The thione (1.0 g, 0.0023 mol) was stirred with an excess of methyl iodide in dry methanol (25 ml) overnight at room temperature. Filtration and recrystallization from ethanol gave 4-methylthio-1-methyl-2,3,5,6-tetraphenylpyridinium iodide (**26**, X = SCH_3; Y = I) as yellow needles: 1.1 g (83%); mp 240–242 °C dec; ir (KBr) 3050 (CH), 1600 cm^{-1} (CN); λ_{max} (CH_3OH) 323 nm (log ϵ 3.93), 248 (4.02); NMR ($CDCl_3$) δ 7.00–7.84 (m, 20, aromatic), 3.60 (s, 3, NCH_3), 1.63 (s, 3, SCH_3).

Anal. Calcd for $C_{31}H_{26}NIS$: C, 65.14; H, 4.59; N, 2.45. Found: C, 64.97; H, 4.38; N, 2.70.

Alkylation of 24 (X = S) with Triethyloxonium Tetrafluoroborate. The thione (0.65 g, 0.0015 mol) in methylene chloride (25 ml) was treated with an excess of triethyloxonium tetrafluoroborate with stirring at room temperature. After 42 h excess anhydrous ether was added. The product was filtered, washed with several portions of anhydrous ether, and recrystallized from ethanol, giving light-yellow needles of 4-ethylthio-1-methyl-2,3,5,6-tetraphenylpyridinium tetrafluoroborate (**26**, X = SEt; Y = BF_4): 0.8 g (100%); mp 293–295 °C; ir (KBr) 3080, 2990, 2950 (CH), 1610 cm^{-1} (C=N); λ_{max} (CH_3OH) 322 nm (log ϵ 4.06), 248 (4.18); NMR ($CDCl_3$) δ 7.00–7.83 (m, 20, aromatic), 3.60 (s, 3, NCH_3), 1.97 (qt, 2, CH_2CH_3), 0.80 (t, 3, CH_2CH_3); mass spectrum *m/e* (rel intensity) 428 (100).

Anal. Calcd for $C_{32}H_{28}NBF_4S$: C, 70.46; H, 5.17; N, 2.57. Found: C, 70.62; H, 5.18; N, 2.55.

Reaction of *N*-Benzoyl-*N*-methyl-*C*-phenylglycine with Triphenylcyclopropene. To *N*-benzoyl-*N*-methyl-*C*-phenylglycine (1.0 g, 0.005 mol) dissolved in acetic anhydride (15 ml) at 40 °C was added triphenylcyclopropene (1.0 g, 0.004 mol) and the reaction mixture heated to 132 °C for 5.5 h. The reaction mixture was cooled, poured into water, and extracted with chloroform. The chloroform layer was extracted in turn with 10% sodium bicarbonate and water, dried over sodium sulfate, and evaporated in vacuo. The residue was either recrystallized from chloroform–ethanol or sublimed (203 °C 1 mm) to yield yellow prisms of 1-methyl-2,3,4,5,6-pentaphenyl-1,4-dihydropyridine (**27**): 0.25 g (14%); mp 206–207 °C (lit.[27] mp 209 °C); ir (KBr) 3050, 2930 cm^{-1} (CH); λ_{max} (CH_3OH) 343 sh nm (log ϵ 3.81), 275 (4.13); NMR ($CDCl_3$) δ 6.93–7.75 (m, 25, aromatic), 4.40 (s, 1, C_4 H), 2.53 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 475 (8).

Anal. Calcd for $C_{36}H_{29}N$: C, 90.91; H, 6.15; N, 2.94. Found: C, 90.83; H, 6.19; N, 2.80.

Registry No.—**1** (R = Ph), 13288-67-0; **1** (R = *p*-ClC_6H_4), 52730-97-9; **4** (R = Ph; X = O), 57550-38-6; **4** (R = *p*-ClC_6H_4; X = O), 57550-39-7; **4** (R = Ph; X = S), 57550-40-0; **4** (R = *p*-ClC_6H_4; X = S), 57550-41-1; **8** (R = Ph), 57587-13-0; **8** (R = *p*-ClC_6H_4), 57550-42-2; **9** (R = Ph), 57550-43-3; **12**, 57550-44-4; **13** (R = Ph), 57550-45-5; **13** (R = *p*-ClC_6H_4), 57550-46-6; **14**, 57550-48-8; **15**, 57550-50-2; **18** (R = Ph), 1280-28-0; **18** (R = *p*-ClC_6H_4), 51787-62-3; **20** (R = Ph), 51787-66-7; **20** (R = *p*-ClC_6H_4), 51787-68-9; **21** (R = Ph), 51787-67-8; **21** (R = *p*-ClC_6H_4), 51808-61-8; **22**, 13712-75-9; **24** (X = O), 51787-63-4; **24** (X = S), 51787-64-5; **26** (X = OEt; Y = BF_4), 51808-60-7; **26** (X = SMe; Y = I), 51787-65-6; **26** (X = SEt; Y = BF_4), 57550-52-4; **27**, 39235-55-7; diphenylcyclopropenone, 886-38-4; $NaBH_4$, 16940-66-2; diphenylcyclopropenethione, 2570-01-6; 2-*p*-chlorophenyl-3,5-diphenyl-4-ethylthio-1-methylpyridinium tetrafluoroborate, 57550-54-6; *N*-benzoyl-*N*-methyl-*C*-phenylglycine, 28544-45-8; methyl iodide, 74-88-4; triphenylcyclopropene, 16510-49-9.

References and Notes

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(29) Criteria for establishing product identity were superimposable infrared spectra, no depression in mixture melting point, and identical R_f values in two different solvent systems.

Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 2. Reactions with Thiopseudoureas and Carbanions

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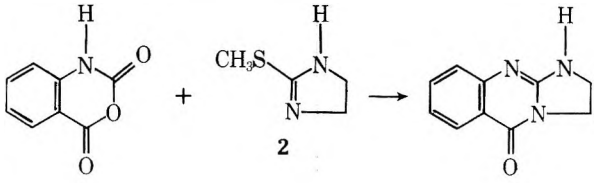
The reaction of 2*H*-3,1-benzoaxazine-2,4(1*H*)-diones with substituted thioureas leads to the formation of 2-aminoquinazolin-1*H*-4-ones. In the case of N-functionalized benzoxazines tricyclic systems are obtained. Carbanions derived from diethyl malonate and activated ethyl acetate derivatives produce substituted quinoline-2,4-diones on reaction with 2*H*-3,1-benzoxazine-2,4(1*H*)-diones.

During the past 30 years several groups have described the use of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride)[1] for the synthesis of quinazolinediones,[2] 4-quinazolinones,[3] pyrroloquinazolinones,[4] and 1,4-benzodiazepine-2,5-diones.[5] Most recently Ziegler[6] and our group[7,8] reported the utilization of isatoic anhydrides in the synthesis of fused quinazolinones, e.g., **3**.[8]

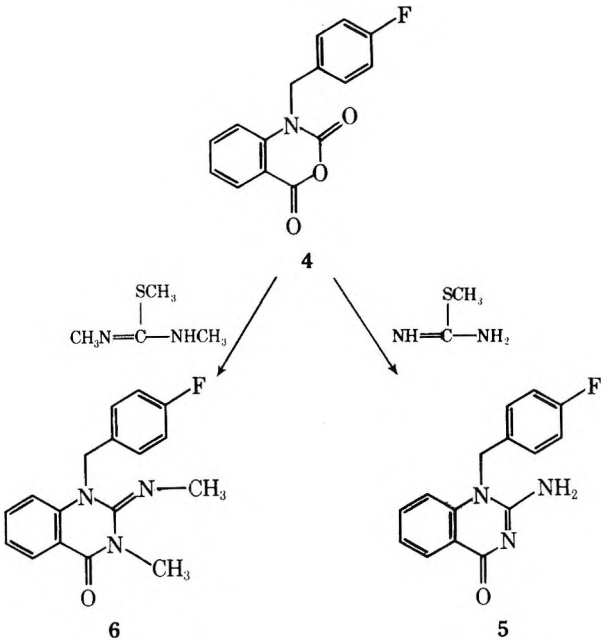


1 **2** **3**

In this publication we wish to report our investigations into the reactions of isatoic anhydrides with thiourea derivatives (Scheme I) and carbanions (Scheme III).

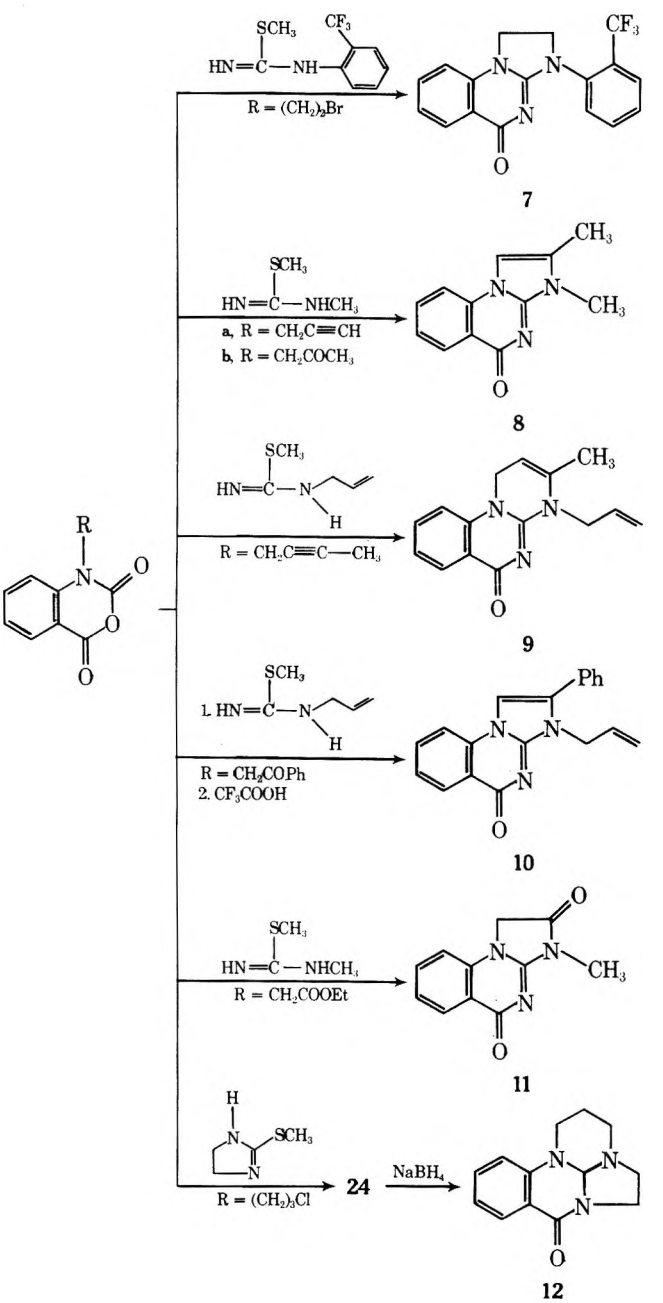
Discussion

Reactions with Thiopseudoureas. During our earlier work we had been concerned with the reaction of isatoic anhydrides with mono- and bicyclic thioureas. In this publication we wish to report some reactions of various isatoic anhydrides we have observed, including those bearing functional groups on the nitrogen atom, with thiopseudoureas (Scheme I). When symmetrically substituted thiopseudoureas are allowed to react with isatoic anhydrides (e.g., **4**) in refluxing dioxane the expected products (**5** or **6**) are isolated in satisfactory yields.



4 **6** **5**

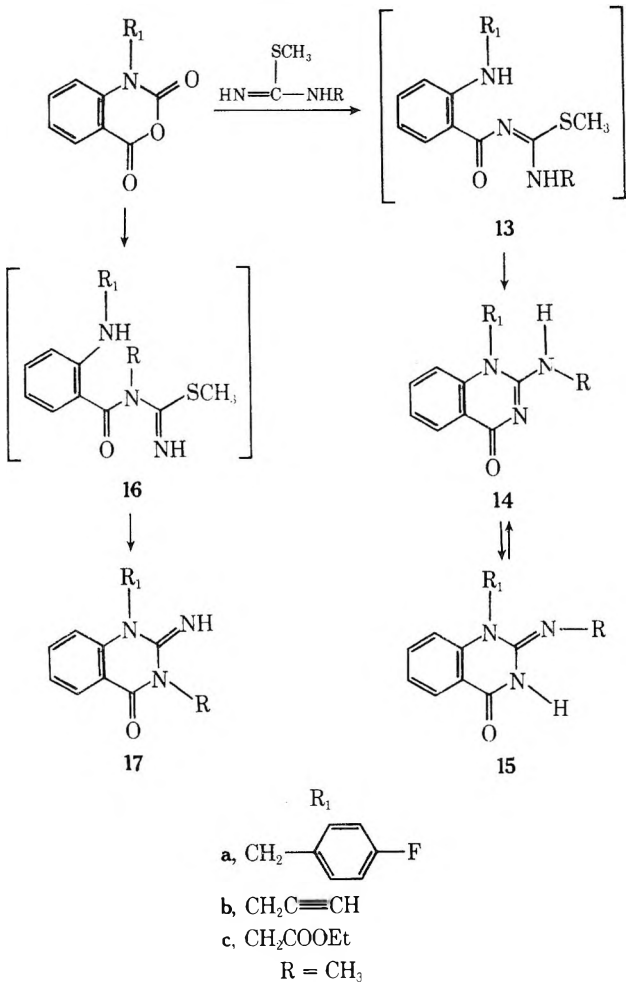
Scheme I



7 **8** **9** **10** **11** **12**

The question arises as to the course of the reaction when unsymmetrically substituted thiopseudoureas are employed (Scheme II). We assume that the initial step of the reaction involves a nucleophilic attack of one of the N atoms of the thiopseudourea onto the isatoic anhydride

Scheme II



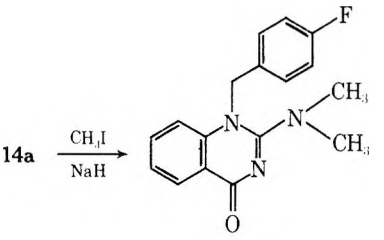
and that the first intermediate collapses, with concomitant loss of carbon dioxide, to yield **13** or **16**. Whether **13** or **16** is the product will depend on which of the N atoms (of the thiopseudourea) reacts with the anhydride. In the case of 2,3-dimethyl-2-thiopseudourea, N-3 might be the more basic nitrogen atom but would, on the other hand, be more sterically hindered during the inital step of the reaction. When 2,3-dialkyl-2-thiopseudoureas were allowed to react with isatoic anhydrides *one* final product **14** or **17** (Scheme II) was isolated. Considering the tautomeric forms in which compounds **14** may exist, interpretation of the NMR spectra did not permit a firm structure assignment. Our hope was therefore to be able to isolate the reaction intermediate **13** or **16** whose spectra might aid us in making an assignment as to the structure of the final product.

By the use of somewhat milder reaction conditions we were able to isolate the otherwise elusive intermediates (**13** or **16**) and fully characterize them in the cases where R_1 = $CH_2C{\equiv}CH$ (**13b**) and CH_2COOEt (**13c**), and R = CH_3. In the NMR spectra of both compounds the *N*-methyl group appeared as a doublet which collapsed to a singlet upon D_2O exchange. This finding strongly suggests that the isatoic anhydride is attacked by the less substituted nitrogen atom of the thiopseudourea and that **13** rather than **16** is the intermediate. It is interesting to note that the appearance of the *N*-methyl peak is also solvent dependent. The doublet is observed when $CDCl_3$ is used, but when the more polar solvent Me_2SO-d_6 is employed, only a singlet is seen. Subsequent cyclization of **13** yields compounds of the general structure **14** or **15**.

The question now arises as to the actual tautomeric form of these products. Upon comparison of the observed infrared carbonyl absorption frequencies with models where the C=N bond is unequivocally exocyclic to the quinazoline ring (namely **6**), it is found that the C=O absorption occurs at 1640 cm^{-1} accompanied by an additional band at 1680 cm^{-1} of almost equal intensity. This second band is assigned to stretching vibrations of the nonconjugated C=N group.[9]

Compounds which do not have an exocyclic C=N bond (e.g., **18**) do not show this second band at 1680 cm^{-1}. We therefore conclude that the reaction products of 2,3-dialkyl-2-thiopseudoureas with isatoic anhydrides exist in the tautomeric structure **14**.

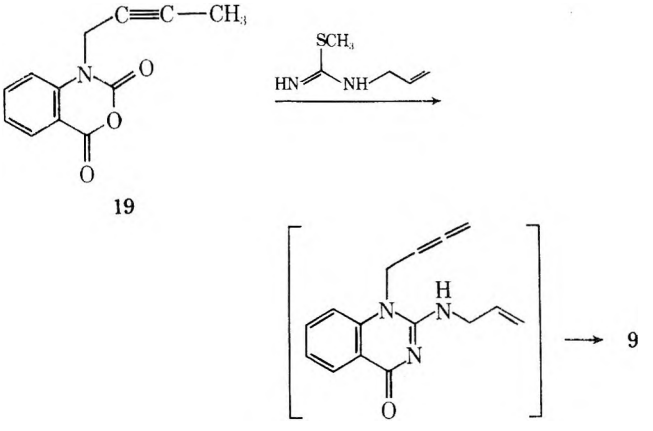
Compound **14a** can be alkylated with methyl iodide in the presence of sodium hydride to produce the *N,N*-dimethyl compound **18**.



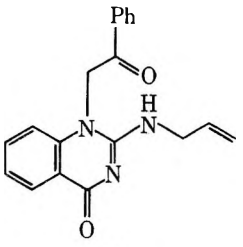
18

Alkylation occurs predominantly on the exocyclic nitrogen, but traces of **6**, formed by alkylation of the ring nitrogen, can be detected in the reaction mixture. As expected, in the NMR spectrum the methyl groups of **18** appear as a singlet whereas those of **6** appear as two distinct singlets. The infrared spectrum of **18** does not show the C=N band at 1680 cm^{-1}, which is in agreement with the conclusions drawn previously concerning product **14**.

In cases where the isatoic anhydride contains a highly reactive functional group on the nitrogen (e.g., 2-chloroethyl) no products of type **14** were isolated. Instead, concomitant reaction of the 2-amino function with the reactive group of the side chain leads to the formation of an additional ring (e.g., **7**). When *N*-(2-propynyl)isatoic anhydride (**27**) was allowed to react with 2,3-dimethyl-2-thiopseudourea in diglyme at reflux temperature, the product which was isolated lacked N–H absorption in its infrared spectrum and the characteristic features of the propynyl group. The appearance in the NMR spectrum of a C-methyl group at δ 2.3 and an olefinic proton at δ 7.5 strongly suggested structure **8**. Similar cyclizations of propynyl groups have been described and an allenic intermediate has been proposed.[10] Interestingly, the homologous isatoic anhydride **19** does not yield the corresponding ethyl analogue of **8**, but rather the six-membered derivative **9**. If indeed this cyclization proceeds through an allenic intermediate, the "terminal" allene **20** should be the precursor.

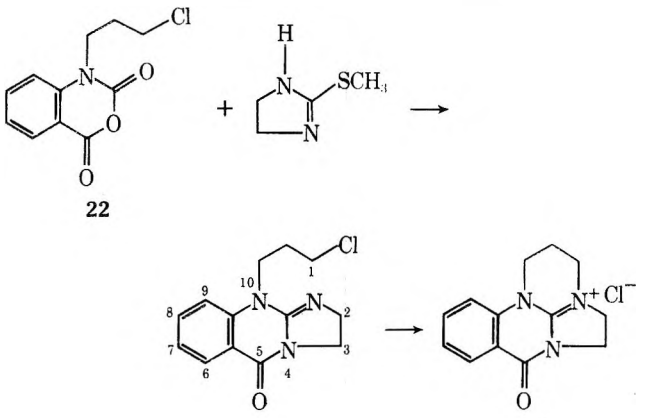


Not unexpectedly, the primary product of the reaction between a 3-allyl-2-methyl-2-thiopseudourea and *N*-phenacylisatoic anhydride was **21**. Treatment with trifluo-



21

roacetic acid transformed **21** into **10** (Scheme I). Having observed the ease of formation of the third ring in compounds such as **7**, we expected that a haloalkyl substituent in the side chain of the isatoic anhydride (e.g., **22**) could quaternize N-1 in the tricyclic intermediate **23** yielding the tetracyclic ammonium salt **24**. The isolation of **23** was not



22 **23** **24**

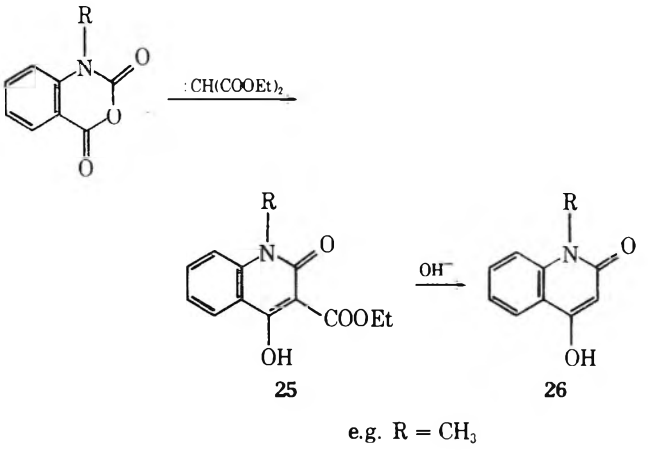
possible, **24** being formed directly. The crude **24** was reduced to **12** in moderate yield with sodium borohydride.

Reactions with Carbanions. To our knowledge the only reported reaction of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione with a β-dicarbonyl compound is that with the anion of ethyl acetoacetate which leads to the formation of 3-carbethoxy-4-hydroxyquinaldine.[11] It was of interest to us to investigate the reactions of other carbanions with this substrate, particularly those of malonates, which should lead to the formation of quinoline-2,4-diones. These are otherwise only accessible through the acid-catalyzed reaction of malonic acid dianilids.[12] This standard method fails, however, in cases where the dianilids are substituted with strongly deactivating groups (e.g., NO_2). Also the *N*-alkylmalonic acid anilids are sometimes difficult to prepare, and reactive or acid-sensitive N substituents will not withstand the vigorous cyclization conditions. Furthermore, *N*-alkylquinoline-2,4-diones cannot be prepared by standard synthetic methods from quinoline-2,4-diones because alkylation occurs preferentially on oxygen, producing 4-alkoxyquinolin-2-ones (**41**, see Experimental Section).

In general we obtained the *N*-alkylquinolinediones (**26**) by allowing the sodium salt of diethyl malonate to react with the corresponding isatoic anhydrides at 120°C in dimethylacetamide followed by alkaline hydrolysis and decarboxylation of the ester group of **25**.

Since various *N*-alkylisatoic anhydrides are readily available[13] and the mildly basic reaction conditions do not interact with potentially reactive groups on the nitrogen, our synthesis avoids most of the difficulties inherent in the standard procedures.

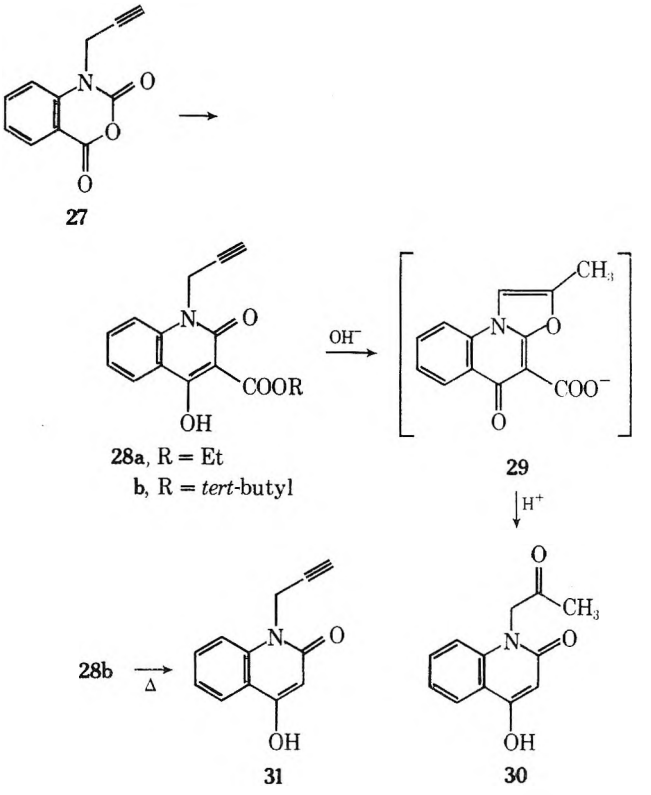
In the case of the *N*-propynyl derivative **28a**, concomi-



25 **26**

e.g. R = CH_3

tant hydration of the acetylenic bond occurred on hydrolysis, yielding **30** probably via the intermediate **29**. This reaction could be circumvented by use of di-*tert*-butyl malonate in the reaction with isatoic anhydride followed by the thermal decarboxylation of ester **28b**, thus giving the desired product **31**.



27

28a, R = Et
b, R = *tert*-butyl

29

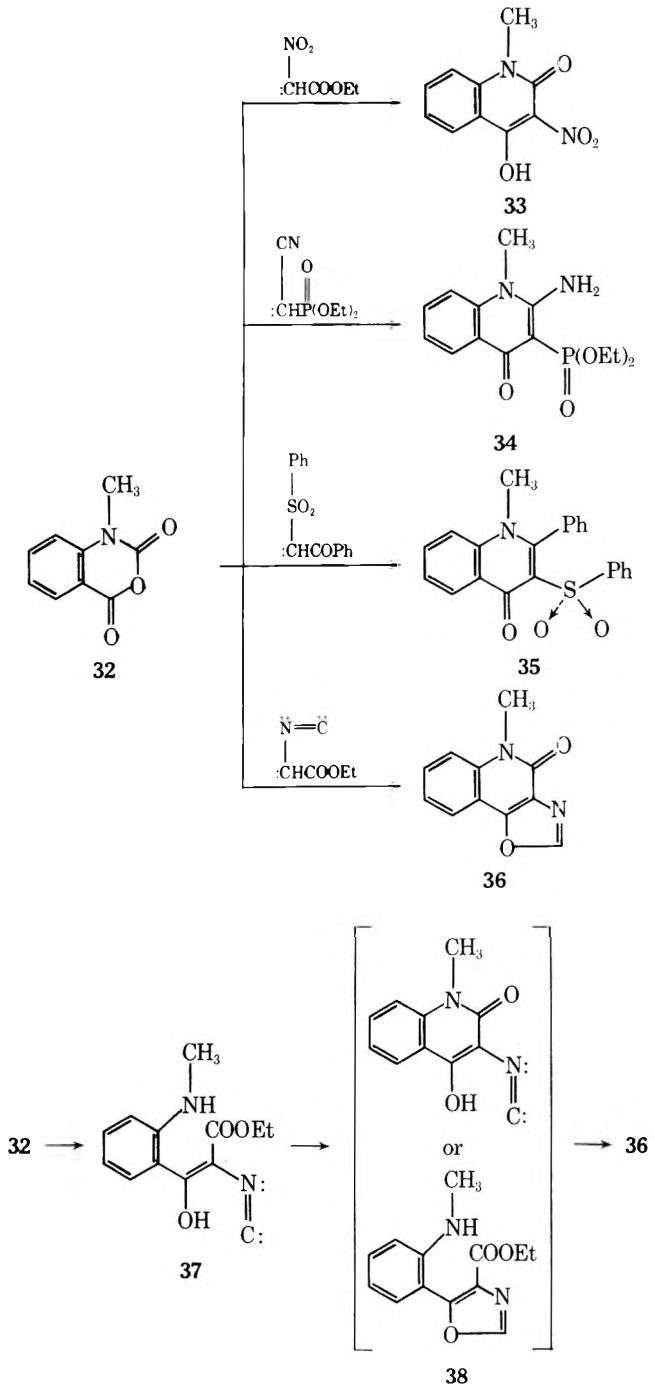
28b **31** **30**

The malonic esters can be replaced by various other compounds possessing an active methylene group and an electrophilic group capable of reacting with the liberated anilino nitrogen. The introduction of nitrogen, sulfur, and phosphorus substituents into the 3 position of the quinoline system can be accomplished by the reaction of isatoic anhydrides with the carbanion of the appropriate nitroacetate, phosphonoacetate, phosphonoacetonitrile, or β-ketosulfones (Scheme III).

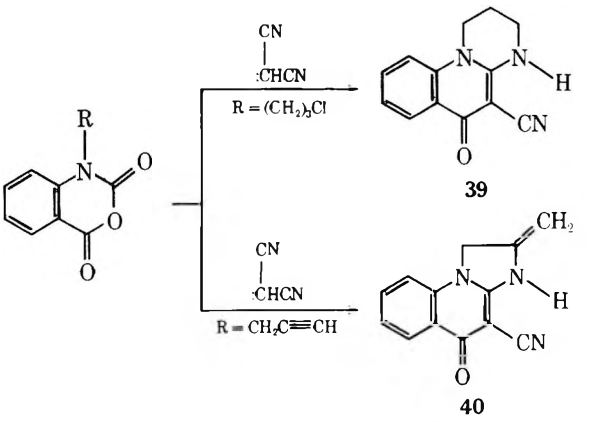
When **32** was treated with ethyl isocyanoacetate, the intermediate **37** spontaneously cyclized to yield **36** whose NMR spectrum ($CDCl_3$–Me_2SO-d_6) showed an olefinic proton at δ 8.4 besides the expected aromatic and methyl protons.

When the sodium salt of malononitrile was allowed to react with *N*-(3-chloropropyl)isatoic anhydride, the pyrimido[1,2-*a*]quinoline (**39**) was isolated (Scheme IV). Similarly, *N*-(2-propynyl)isatoic anhydride yielded the tricyclic

Scheme III



Scheme IV



product **40**. Contrary to our earlier observation (namely, the formation of **8**), the carbon–carbon double bond in the imidazole portion of this cyclization product was found to be exocyclic to the ring, as evident from the presence of a methylene group at δ 3.5 and two vinylic protons at δ 5.2 in the NMR spectrum.

Further investigations are presently being conducted into the formation of new heterocyclic ring systems using functionalized isatoic anhydrides.

Experimental Section[14]

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. NMR spectra were determined on Varian A-60 and T-60 spectrophotometers using Me_4Si as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over Na_2SO_4. No attempt has been made to optimize the yields of the described reactions.

Procedure A (Preparation of Intermediates of Type 13). A suspension of 0.1 mol of the appropriate N-substituted isatoic anhydride, 0.1 mol of a 2,3-disubstituted 2-thiopseudourea hydriodide, and 11.7 g (0.11 mol) of Na_2CO_3 in 300 ml of CH_3CN was refluxed for 30 min. The solvent was removed under reduced pressure, and the residue suspended in 100 ml of CH_2Cl_2. The insoluble material was filtered off and washed twice with 50 ml of CH_2Cl_2. The solvent was exchanged for CH_3OH; and, upon cooling, crystallization occurred. The product was filtered, washed with Et_2O, and dried.

Procedure B (Cyclization of Intermediates of Type 13). A solution of 0.05 mol of intermediate **13** in 100 ml of diglyme was refluxed for 2 h (catalyzed by one pellet of NaOH). Upon cooling to room temperature, precipitation occurs. The resulting solid was filtered, washed with a small amount of EtOAc, and recrystallized from CH_2Cl_2 or CH_3OH.

Procedure C (Preparation of Quinazolin-4-ones from Substituted Isatoic Anhydrides). A suspension of 0.1 mol of the appropriate N-substituted isatoic anhydride, 0.1 mol of a 2,3-disubstituted 2-thiopseudourea hydriodide, and 11.7 g (0.11 mol) of Na_2CO_3 in 300 ml of CH_3CN was refluxed for 30 min. The solvent was removed under pressure, and the residue suspended in 100 ml of CH_2Cl_2. The insoluble salts were filtered off and washed twice with 50 ml of CH_2Cl_2. The CH_2Cl_2 was then replaced by 150 ml of diglyme and the reaction mixture (catalyzed by one pellet of NaOH) was heated under reflux for 2 h. Upon cooling to room temperature, precipitation occurs. The resulting solid was filtered, washed with a small amount of EtOAc, and recrystallized from CH_2Cl_2 or CH_3OH.

1-(*p*-Fluorobenzyl)-2-aminoquinazolin-1*H*-4-one (5). Using procedure C, 27.1 g (0.1 mol) of *N*-(*p*-fluorobenzyl)isatoic anhydride (**4**) and 21.8 g (0.1 mol) of 2-methyl-2-thiopseudourea hydriodide yielded 11.9 g of **5** (44%): mp 265–267°; ir (KBr) 3330, 3170, 1600 cm^{-1}; NMR (Me_2SO) δ 8.0 (m, 1), 7.3 (m, 9), 5.4 (s, 2).

Anal. Calcd for $C_{15}H_{12}N_3OF$: C, 66.9; H, 4.5; N, 15.6. Found: C, 67.0; H, 4.6; N, 15.4.

2,3-Dihydro-1-(*p*-fluorobenzyl)-3-methyl-2-methylimino-4-(1*H*)-quinazolinone (6). Using procedure C, 27.1 g (0.1 mol) of **4** and 24.6 g (0.1 mol) of 1,2,3-trimethyl-2-thiopseudourea hydriodide yielded 13.1 g of **6** (44%): mp 71–73°; ir ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (m, 1), 7.1 (m, 7), 5.2 (s, 2), 3.5 (s, 3), 3.3 (s, 3).

Anal. Calcd for $C_{17}H_{16}N_3OF$: C, 68.7; H, 5.4; N, 14.1. Found: C, 68.5; H, 5.5; N, 14.1.

2,3-Dihydro-3-(2-trifluoromethylphenyl)imidazo[1,2-*a*]-quinazolin-5(1*H*)-one (7). Using procedure C, 24.0 g of (2-bromoethyl)isatoic anhydride and 36.2 g of 3-(o-trifluoromethylphenyl)-2-methyl-2-thiopseudourea[15] yielded 8.6 g of **7** '(free base) (26%): mp 222–224°; ir (KBr) 1605 cm^{-1}; NMR (Me_2SO) δ 7.6 (m, 8), 4.2 (m, 4).

Anal. Calcd for $C_{17}H_{12}N_3OF_3$: C, 61.6; H, 3.7; N, 12.7. Found: C, 61.5; H, 4.1; N, 12.9.

2,3-Dimethylimidazo[1,2-*a*]quinazolin-5(3*H*)-one (8). A. Using procedure B, **13b** yielded 5.3 g of **8** (49%): mp 237–240°; ir ($CHCl_3$) 1610 cm^{-1}; NMR (Me_2SO) δ 8.1 (m, 1), 7.8 (m, 3), 7.5 (m, 1), 3.4 (s, 3), 2.3 (d, 3).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.6; H, 5.2; N, 19.7. Found: C, 67.3; H, 5.2; N, 19.9.

B. Using procedure C, *N*-acetonylisatoic anhydride and 2,3-di-

methyl-2-thiopseudourea hydriodide yielded 5.8 g of 8 (27%). All physical constants and spectra were identical with those from the above route.

4-Allyl-3-methyl-1,4-dihydro-6*H*-pyrimido[1,2-*a*]quinazolin-6-one (9). Using procedure C, 21.5 g of *N*-(2-butynyl)isatoic anhydride and 25.8 g of 3-allyl-2-methyl-2-thiopseudourea hydriodide[16] yielded 5.1 g of **9** (20%): mp 131–135°; ir ($CDCl_3$) 1640 cm^{-1}; NMR (CF_3COOH) δ 8.0 (m, 5), 5.9 (m, 1), 5.5 (m, 2), 5.0 (d, 2), 4.4 (t, 2), 1.9 (s, 3).

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.1; H, 6.0; N, 16.6. Found: C, 70.8; H, 6.3; N, 16.6.

3-Allyl-2-phenylimidazo[1,2-*a*]quinazolin-5(3*H*)-one (10). A solution of 6.4 g (0.02 mol) of **21** in 40 ml of CF_3COOH was stirred at room temperature for 30 min. The solution was evaporated to dryness and the residue was dissolved in 100 ml of 2 N aqueous NaOH. The solution was extracted three times with 50 ml of CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting solid was recrystallized from CH_2Cl_2–Et_2O to yield 5.4 g of **10** (89%): mp 198–200°, ir (KBr) 1595 cm^{-1}; NMR (CF_3COOH) δ 8.7 (m, 1), 8.1 (m, 4), 7.7 (s, 5), 6.0 (m, 1), 5.5 (d, 2), 5.0 (d, 2).

Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.7; H, 5.0; N, 14.0. Found: C, 75.9; H, 5.0; N, 13.7.

3-Methylimidazo[1,2-*a*]quinazoline-2,5(1*H*,3*H*)-dione (11). Using procedure B, **13c** yielded 6.2 g of **11** (28%): mp 285–288°; ir (KBr) 1620 cm^{-1}; NMR (CF_3COOH) δ 8.5–7.4 (m, 4), 5.2 (s, 2), 3.6 (s, 3).

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.4; H, 4.2; N, 19.5. Found: C, 61.3; H, 4.4; N, 19.6.

2,3,4,4a-Tetrahydro-1*H*-4,5-ethanopyrimido[1,2-*a*]quinazolin-6-(5*H*)-one (12). A solution of 12 g (0.05 mol) of **22**, 5.8 g (0.05 mol) of 2-methylthio-2-imidazoline, and a catalytic amount of KOH in 250 ml of dioxane was refluxed for 2.5 h. Upon cooling to room temperature the resulting precipitate (**24**) was filtered, washed with Et_2O, and dissolved in 200 ml of 50% aqueous EtOH. This was then added to a solution of 2.4 g of sodium borohydride in 40 ml of 80% EtOH at −15° and the mixture was stirred at −10° for 30 min. After 200 ml of cold H_2O was added to the mixture, the solvent was concentrated to 50 ml under reduced pressure. The resulting precipitate was filtered, washed with H_2O, and recrystallized from CH_2Cl_2–Et_2O to yield 3.7 g of **12** (32%): mp 144–146°; ir ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$) δ 7.9 (m, 1), 7.0 (m, 3), 4.5 (s, 1), 4.1–1.5 (m, 10).

Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.6; N, 18.3. Found: C, 68.3; H, 6.6; H, 18.6.

1-[2-(*p*-Fluorobenzylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13a). Using procedure A, 27.3 g of **4** and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 23.6 g of **13a** (73%): mp 101–102°, ir ($CHCl_3$) 3320, 1620 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (m, 1), 8.4 (m, 1), 6.9 (m, 7), 4.4 (d, 2), 3.0 (d, 3) 2.4 (s, 3).

Anal. Calcd for $C_{17}H_{18}N_3OSF$: C, 60.2; H, 5.7; N, 13.2; S, 10.0. Found: C, 60.1; H, 5.8; N, 12.8; S, 9.9.

1-[2-(2-Propynylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13b). Using procedure A, 20.1 g of *N*-(2-propynyl)isatoic anhydride (**27**) and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 23.9 g of **13b** (91%): mp 93–96°, ir ($CHCl_3$) 3300, 1615 cm^{-1}; NMR ($CDCl_3$) δ 8.7 (t, 1), 8.1 (m, 1), 7.3 (m, 1), 6.7 (m, 2), 4.0 (q, 2), 3.3 (m, 1), 3.0 (m, 4), 2.4 (s, 3).

Anal. Calcd for $C_{13}H_{15}N_3OS$: C, 59.7; H, 5.8; N, 16.1; S, 12.3. Found: C, 59.8; H, 5.7; N, 15.7; S, 11.9.

1-[2-(Ethoxycarbonylmethylamino)benzoyl]-2,3-dimethyl-2-thiopseudourea (13c). Using procedure B, 24.9 g of *N*-ethoxycarbonylmethylisatoic anhydride and 23.2 g of 2,3-dimethyl-2-thiopseudourea hydriodide yielded 28.7 g of **13c** (93%): mp 67–70°; ir ($CHCl_3$) 1750, 1620 cm^{-1}; NMR ($CDCl_3$) δ 10.8 (m, 1), 9.0 (m, 1), 8.3 (m, 1), 7.3 (m, 1), 6.5 (m, 2), 4.2 (m, 4), 3.0 (d, 3), 2.5 (s, 3), 1.2 (t, 3).

Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.3; H, 6.1; N, 13.6; S, 10.4. Found: C, 54.3; H, 6.5; N, 14.1; S, 10.9.

1-(*p*-Fluorobenzyl)-2-methylaminoquinazolin-1*H*-4-one (14a). Using procedure B, **13a** yielded 11.1 g of **14a** (74%): mp 253–256°; ir (KBr) 3250, 1600 cm^{-1}; NMR (Me_2SO) δ 8.1 (m, 1), 7.3 (m, 8), 5.4 (s, 2), 2.9 (d, 3).

Anal. Calcd for $C_{16}H_{14}N_3OF$: C, 67.8; H, 5.0; N, 14.8. Found: C, 67.6; H, 5.2; N, 14.7.

1-(*p*-Fluorobenzyl)-2-dimethylaminoquinazolin-1*H*-4-one (18). To a suspension of 0.4 g of NaH (57%, pentane washed) in 30 ml of dimethylacetamide was added 2.83 g (0.01 mol) of **14a** in portions. After the evolution of hydrogen ceased 1.55 g (0.011 mol) of CH_3I was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured onto ice–water and the resulting precipitate was filtered off (this was found to be mostly **6**). The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated and upon the addition of Et_2O furnished 1.15 g of **18** (38%): mp 166–170°; ir ($CHCl_3$) 1645 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.0 (m, 1), 7.1 (m, 7), 5.25 (s, 2), 3.0 (s, 6).

Anal. Calcd for $C_{17}H_{16}N_3OF$: C, 68.7; H, 5.4; N, 14.1. Found: C, 68.8; H, 5.6; N, 14.2.

2-Allylamino-1-phenacylquinazolin-4(1*H*)-one (21). Using procedure C, *N*-phenacylisatoic anhydride and 3-allyl-2-methyl-2-thiopseudourea hydriodide yielded 16.6 g of **21** (52%): mp 245° dec; ir (KBr) 3060, 1610 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.4; H, 5.4; N, 13.2. Found: C, 71.4; H, 5.2; N, 13.0.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (25). To a solution of 21.0 g (0.13 mol) of diethyl malonate in 75 ml of dimethylacetamide was added 5.3 g (0.13 mol) of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min and was placed in an oil bath at 80°. To this a solution of 22.0 g (0.125 mol) of **32** in 125 ml of dimethylacetamide was added dropwise over a period of 15 min (CO_2 evolution occurs). The mixture was stirred at 120° for 18 h. The resulting precipitate was filtered, washed twice with Et_2O, and then dissolved in 600 ml of warm H_2O. After treatment with charcoal, the solution was acidified with 6 N HCl and the precipitate was filtered, washed with water, and crystallized from CH_2Cl_2–Et_2O to yield 20.5 g of **25** (67%): mp 100–102°; ir ($CHCl_3$) 1650, 1625 cm^{-1}; NMR ($CDCl_3$) δ 12.9 (s, 1), 8.1 (m, 1), 7.8–7.1 (m, 3), 4.5 (q, 2), 3.6 (s, 3), 1.5 (t, 3).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.2; H, 5.6; N, 5.4.

4-Hydroxy-1-methyl-2(1*H*)-quinolinone (26). A mixture of 2.0 g (0.008 mol) of **25** in 40 ml of 2 N aqueous NaOH was refluxed for 3 h. The resulting solution was cooled and acidified with 6 N HCl. Precipitation and CO_2 evolution occurred. The precipitate was filtered, washed well with water, and dried in vacuo to yield 1.2 g of **26** (86%), mp 266–270° (lit.[12] mp 265°).

1,2-Dihydro-4-hydroxy-1-(2-propynyl)-2-oxo-3-quinolinecarboxylic Acid Ethyl Ester (28a). Using the procedure for **25**, but a reaction time of 4 h, 8.0 g (0.04 mol) of **27** and 6.5 g (0.04 mol) of diethyl malonate yielded 7.8 g of **28a** (70%): mp 171–174°; ir ($CHCl_3$) 3330, 1665, 1635 cm^{-1}; NMR ($CDCl_3$) δ 14.4 (s, 1), 8.25 (m, 1), 7.5 (m, 3), 5.1 (d, 2), 4.5 (q, 2), 2.25 (t, 1), 1.5 (t, 3).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.3; H, 5.0; N, 4.8.

1,2-Dihydro-4-hydroxy-1-(2-propynyl)-2-oxo-3-quinolinecarboxylic Acid *tert*-Butyl Ester (28b). Using the procedure for **25** but a reaction time of 5 h, 21.0 g (0.105 mol) of **27** and 25.0 g (0.115 mol) of di-*tert*-butyl malonate yielded 18.0 g of **28b** (57%): mp 168–170°; ir ($CHCl_3$) 3300, 1650, 1620 cm^{-1}; NMR ($CDCl_3$) δ 14.6 (s, 1), 8.25 (m, 1), 7.5 (m, 3), 5.05 (d, 2), 2.25 (t, 1), 1.7 (s, 9).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.0; H, 5.9; N, 4.6.

1-Acetonyl-4-hydroxy-2(1*H*)-quinolinone (30). A mixture of 7.7 g of **28a** in 125 ml of 2 N NaOH was refluxed for 90 min. The resulting solution was cooled and acidified with 6 N HCl (precipitation and CO_2 evolution occurred). The precipitate was filtered, washed well with water, and dried in vacuo to yield 5.5 g of **30** (90%): mp 257–260°; ir (Nujol) 1720, 1640 cm^{-1}; NMR (Me_2SO) δ 11.6 (s, broad, 1), 8.0 (m, 1), 7.4 (m, 3), 5.95 (s, 1), 5.2 (s, 2), 2.25 (s, 3).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.4. Found: C, 66.0; H, 4.8; N, 6.3.

4-Hydroxy-1(2-propynyl)-2(1*H*)-quinolinone (31). A suspension of 5.0 g of **28b** in 85 ml of *o*-dichlorobenzene was heated slowly from 100 to 170° (a solution forms) and was kept at 170° for 2 h (when the temperature reached 170° gas evolution begins and a precipitate forms). The reaction mixture was cooled and the precipitate was filtered, washed with Et_2O, and recrystallized from MeOH to yield 3.0 g of **31** (90%): mp 211–214°; ir (Nujol) 3290, 1650 cm^{-1}; NMR (Me_2SO) δ 11.1 (s, broad, 1), 8.0 (m, 1), 7.5 (m, 3), 5.9 (s, 1), 5.1 (d, 2), 3.2 (t, 1).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.4; H, 4.5; N, 7.0. Found: C, 72.0; H, 4.8; N, 6.7.

4-Hydroxy-1-methyl-3-nitro-2(1*H*)-quinolinone (33). The reaction was carried out similarly to that of compound **25**. The solvent from the reaction mixture was removed under reduced pressure, and the residue was dissolved in H_2O. After acidification with 6 N HCl the resulting precipitate was filtered, washed with water,

and recrystallized from CH_2Cl_2–Et_2O to yield **33** (42%): mp 169–170°; ir ($CHCl_3$) 1670, 1630, 1540, 1430 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 11.3 (s, broad, 1), 8.1 (m, 1), 7.9–7.1 (m, 3), 3.65 (s, 3).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.6; H, 3.7; N, 12.7. Found: C, 54.3; H, 3.9; N, 12.4.

(2-Amino-1,4-dihydro-1-methyl-4-oxoquinolin-3-yl)phosphonic Acid Diethyl Ester (34). To a solution of 8.8 g (0.05 mol) of diethyl cyanomethylphosphonate in 75 ml of dimethylacetamide, 2.1 g (0.05 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 8.8 g (0.05 mol) of **32** in 75 ml of dimethylacetamide was then added. The resulting mixture was placed in an oil bath, and the temperature was raised slowly to 120° and kept there for 4 h (CO_2 evolution occurs). The solvent was removed under reduced pressure, and water was added to the residue. The mixture was extracted into EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to produce 15 g of an oil which was readily crystallized from Et_2O to yield 11.4 g of **34** (74%): mp 193–196°; ir ($CHCl_3$) 3490, 3300, 3140, 1620, 1570, 1510 cm^{-1}; NMR ($CDCl_3$) δ 8.3 (m, 1), 8.1 (s, 2), 7.8–7.1 (m, 3), 4.2 (m, 4), 3.8 (s, 3), 1.3 (t, 6).

Anal. Calcd for $C_{14}H_{19}N_2O_4P$: C, 54.2; H, 6.2; N, 9.0. Found: C, 53.8; H, 6.2; N, 9.0.

1-Methyl-2-phenyl-3-phenylsulfonylquinolin-4(1*H*)-one (35). To a solution of 10.0 g (0.038 mol) of phenyl phenacylsulfone in 100 ml of dimethylacetamide, 1.85 g (0.038 mol) of NaH (50%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min and placed in an oil bath at 120°. To this, a solution of 6.8 g (0.038 mol) of **32** in 50 ml of dimethylacetamide was added dropwise over a period of 10 min (CO_2 evolution occurs). The mixture was stirred at 120° for 18 h. The solvent was removed under reduced pressure, and water was added to the residue. The resulting precipitate was washed twice with water and recrystallized from CH_2Cl_2–Et_2O to yield 5.2 g of **35** (36%): mp 268–270°; ir ($CHCl_3$) 1620, 1600, 1390, 1160, 1145 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.3 (m, 1), 8.0–7.3 (m, 13), 3.4 (s, 3).

Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.4; H, 4.6; N, 3.7; S, 8.5. Found: C, 70.0; H, 4.8; N, 3.6; S, 8.5.

5-Methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (36). To a solution of 5.7 g (0.05 mol) of ethyl isocyanoacetate[17] in 75 ml of dimethylacetamide, 2.1 g (0.05 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 8.8 g (0.05 mol) of **32** in 75 ml of dimethylacetamide was then added. The resulting mixture was placed in an oil bath. The temperature was raised slowly to 120° and kept there for 5 h (CO_2 evolution occurs). The solvent was removed under reduced pressure, and H_2O was added to the residue. The resulting precipitate was filtered, washed well with H_2O, and crystallized from CH_2Cl_2–Et_2O to yield 2.6 g of **36** (45%): mp 191–194°; ir ($CHCl_3$) 1670, 1585 cm^{-1}; NMR ($CDCl_3$–Me_2SO) δ 8.4 (s, 1) 8.0–7.2 (m, 4), 3.8 (s, 3).

Anal. Calcd for $C_{11}H_8N_2O_2$, C, 66.0; H, 4.0; N, 14.0. Found: C, 66.1; H, 4.0; N, 14.1.

5-Cyclopropylmethyloxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, *N*-cyclopropylmethylisatoic anhydride[13] and ethyl isocyanoacetate yielded 38% of product, mp 164–167°.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.6; H, 5.3; N, 11.6.

8-Chloro-5-methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, 6-chloro-1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione and ethyl isocyanoacetate yielded 33% of product mp 210–213°.

Anal. Calcd for $C_{11}H_7N_2O_2Cl$: C, 56.3; H, 3.0; N, 11.9; Cl, 15.1. Found: C, 55.9; H, 3.3; H, 11.7; Cl, 15.2.

5-Methyl-7,8-methylenedioxyoxazolo[4,5-*c*]quinolin-4(5*H*)-one. Using the procedure for that of compound **36**, 1-methyl-6,7-methylenedioxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione[13] and ethyl isocyanoacetate yielded 35% product, mp >310°.

Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.3; N, 11.5. Found: C, 58.8; H, 3.5; N, 11.4.

2,3,4,6-Tetrahydro-6-oxo-1*H*-pyrimido[1,2-*a*]quinoline-5-carbonitrile (39). To a solution of 1.4 g (0.021 mol) of malononitrile in 20 ml of dimethylacetamide, 0.9 g (0.021 mol) of NaH (57%, pentane washed) was added in portions. When the evolution of hydrogen ceased, the solution was stirred for 15 min. A solution of 5.0 g (0.021 mol) of **22**[13] in 45 ml of dimethylacetamide was then added dropwise over a period of 30 min. The mixture was stirred at room temperature for 30 min, then at 120° for 18 hr (CO_2 evolution occurs). The mixture was then poured on H_2O. The resulting precipitate was filtered and washed with H_2O, MeOH, and Et_2O to yield 2.7 g of **39** (58%). A sample was crystallized from EtOAc: mp 267–269°; ir (Nujol) 3300, 2200, 1600, 1550, 1460 cm^{-1}; NMR (Me_2SO) δ 8.15 (m, 1), 7.8–7.2 (m, 4), 4.3 (m, 2), 3.85 (t, 2), 2.2 (m, 2).

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.0; H, 5.1; N, 18.8.

1,2,3,5-Tetrahydro-2-methylene-5-oxoimidazo[1,2-*a*]quinoline-4-carbonitrile (40). To a solution of 1.7 g (0.026 mol) of malononitrile in 20 ml of dimethylacetamide was added 1.1 g (0.026 mol) of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, a solution of 5.0 g (0.025 mol) of **27**[13] in 30 ml of dimethylacetamide was added dropwise over a period of 5 min. The mixture was stirred at room temperature for 15 min and then at 120° for 2 h. The reaction mixture was concentrated to one-fourth volume and was poured onto 100 ml of cold H_2O. The solution was acidified with 2 N HCl and the resulting precipitate was filtered, washed with H_2O, and triturated with hot EtOH to yield 4.5 g of **40** (82%): mp 285° (then resolidifies); ir (Nujol) 3340, 3200, 2210, 1680 cm^{-1}; NMR (Me_2SO) δ 8.2 (m, 1), 8.0–7.3 (m, 4), 5.2 (d, 2), 3.5 (s, 2).

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.9; H, 4.1; N, 18.8. Found: C, 70.2; H, 4.0; N, 18.5.

4-Ethoxy-2(1*H*)-quinolinone (41). To a suspension of 6.0 g of 2,4-quinolinediol in 50 ml of dimethylacetamide was added 1.6 g of NaH (57%, pentane washed) in portions. When the evolution of hydrogen ceased, 6.0 g of ethyl iodide was added. The mixture was stirred at 30–35° for 5 min and then at room temperature for 18 h. The resulting precipitate was filtered and crystallized from MeOH to yield 2.8 g of **41** (40%): mp 223–226°; ir (Nujol) 1640 cm^{-1}; NMR (Me_2SO) δ 11.6 (s, broad, 1), 7.5 (m, 4), 6.0 (s, 1), 4.3 (q, 2), 1.5 (t, 3).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9; N, 7.4. Found: C, 69.9; H, 5.5; N, 7.3.

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References and Notes

(1) Throughout this paper the names "isatoic anhydride" and "2*H*-3,1-benzoxazine-2,4(1*H*)-dione" are used interchangeably. Commercial sources still prefer the first name whereas *Chemical Abstracts* subscribes to the latter. We have adopted the *Chemical Abstracts* numbering system for substituted isatoic anhydrides, but we feel that it will be easier to read if we use the expression "N-substituted isatoic anhydride" rather than "N-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-dione".

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(14) No attempts were made to optimize yields of the reactions.
(15) Prepared in 93% yield by the alkylation of 2-thio-1-(α,α,α-trifluoro-*o*-tolyl)urea [F. Kurzer and J. Canell, *Tetrahedron*, **19**, 1603 (1963)] with methyl iodide in ethanol. The material was used without further purification.
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Thermal Decomposition of 2*H*-Azirines. Formation of Products Resulting from Carbon–Carbon Bond Cleavage[1]

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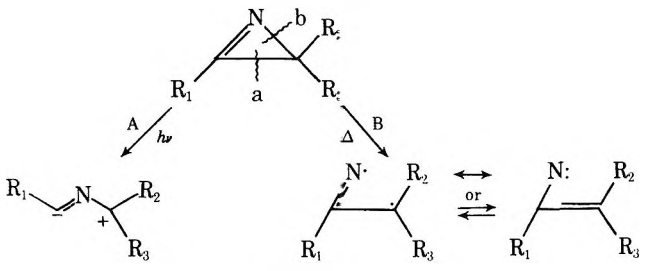
The synthesis and thermal decomposition of 2-methyl-3-phenyl- (**19a**), 2-ethyl-3-phenyl- (**19b**), 2,2-dimethyl-3-phenyl- (**19c**), and 2,3-dimethyl-2-phenyl-2*H*-azirines (**19d**) is described. Previously, products formed on thermal decomposition of 2*H*-azirines have been derived from initial C–N bond cleavage; in contrast, the products observed on heating **19a–c** (styrenes, benzonitrile, and HCN or acetonitrile) are formed by C–C cleavage, leading initially to iminocarbene intermediates. Evidence is presented that the primary mode of product formation from such an intermediate is 1,4-hydrogen shift, giving a 2-azabutadiene. The azabutadiene then fragments (via a small equilibrium concentration of substituted 1-azacyclobutene) leading to the final products. At higher temperatures, the azabutadienes are converted to dihydroisoquinolines as well.

Photochemical and thermal bond cleavage preferences in 2*H*-azirines appear to be quite distinct. Products formed during photochemical isomerizations appear to always involve carbon–carbon bond cleavage (path A, Scheme I), while thermal isomerization products arise from initial carbon–nitrogen bond cleavage (path B, Scheme I).

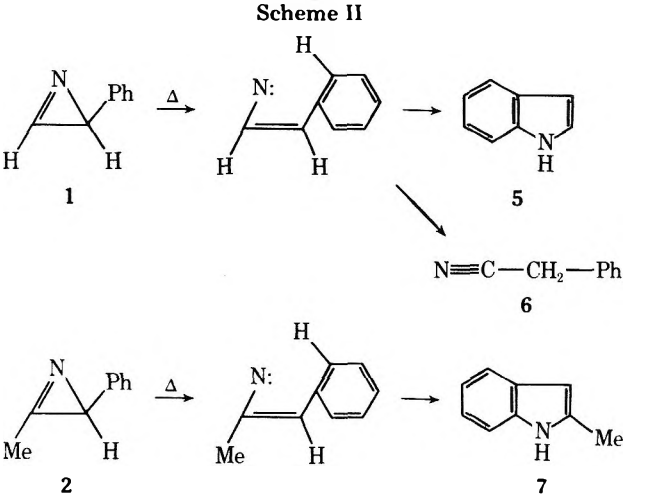
Scheme I



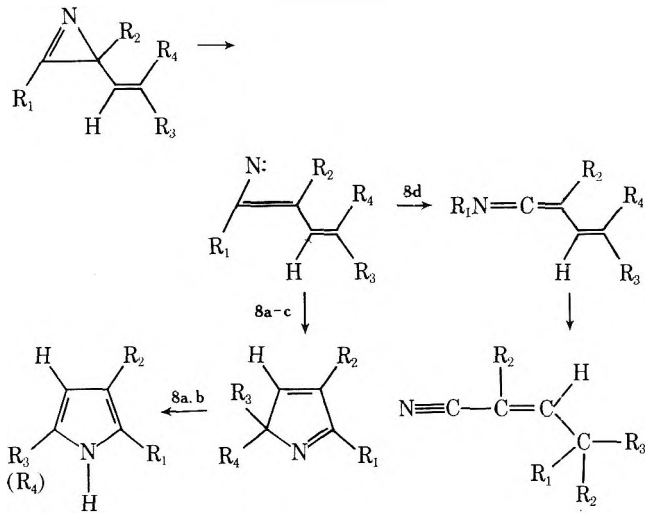
Azirine photochemistry has been extensively investigated by several groups. Padwa[3] and Schmid,[4] for example, have shown in independent studies that upon photolysis 3-phenyl-2*H*-azirines undergo cycloadditions with a variety of 1,3-dipolarophiles. These reactions apparently all proceed by initial C–C cleavage in the azirines, leading to dipolar species. Schmid and co-workers have also photolyzed triphenyl-2*H*-azirine in a 2,2-dimethylbutane–pentane matrix at −185 °C and observed a new uv maximum at ca. 350 nm ($\epsilon \sim 10^4$). The authors assigned this band to a nitrile ylide species. They further showed that the ylide rearranged to starting azirine only photochemically, and were able to trap it at low temperatures using methyl trifluroacetate. Recent ab initio MO calculations by Salem,[5] utilizing a configuration interaction treatment, suggest that upon cleaving a C–C azirine bond, the ground state nitrile ylide energy surface is best reached by internal conversion from a singlet n,π^* state at a C–N–C bond angle of 100°. Salem's calculations also predict a large barrier for thermal conversion of the ylide to azirine, but suggest a facile photochemical conversion.

Relative to the well-defined photochemistry of 2*H*-azirines, their thermal behavior is not as well understood. The first report of a 2*H*-azirine pyrolysis was made by Isomura and co-workers in 1968.[6] These workers prepared 2-phenyl-2*H*-azirine (**1**) and 3-methyl-2-phenyl-2*H*-azirine (**2**) by photolytic and thermal decomposition of *cis*- and *trans*-1-azido-2-phenylethene (**3c** and **3t**) and *cis*- and *trans*-2-azido-1-phenylpropene (**4c** and **4t**), respectively. Thermal decomposition of **1** in boiling hexadecane yielded a 1:1 mixture of indole (**5**) and phenylacetonitrile (**6**) in 86% isolated yield. Similar treatment of **2** gave only 2-methylindole (**7**). The most obvious mechanism for formation of **5**, **6**, and **7** involved a vinyl nitrene intermediate generated by rupture of the *carbon–nitrogen* bond, followed by insertion into the phenyl group or α-carbon–hydrogen bond (see Scheme II).

Scheme II



Scheme III

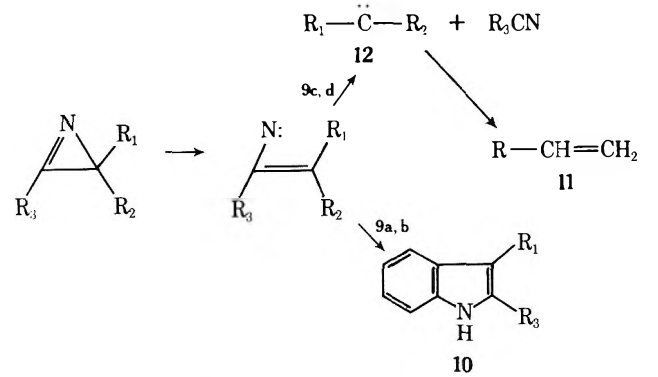


	R_1	R_2	R_3	R_4
8a	H	H	Ph	H
b	H	Ph	H	CH_3
c	CH_3	Ph	Ph	Ph
d	H	Ph	Ph	Ph

In 1972, the Isomura research group published a study of the thermal rearrangements in dilute solution of a series of 2-vinyl-2*H*-azirines.[7] The results of this study, which can again be explained by C–N cleavage leading to a vinyl nitrene, are displayed in Scheme III.

Rees and co-workers have subjected the series of 2*H*-azirines **9a–d** to flash-vacuum pyrolysis at 400–500 °C.[8] Their results may also be accounted for by initial carbon–nitrogen bond cleavage (Scheme IV). Nishiwaki and co-workers[9]

Scheme IV

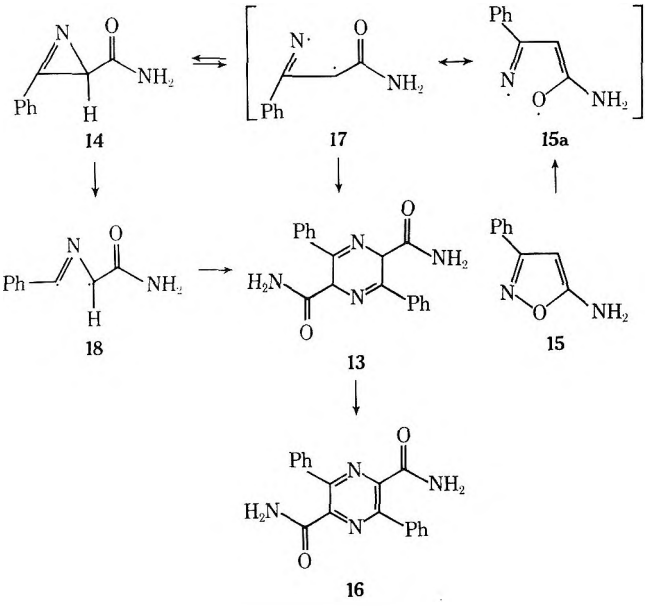


9a, R_1 = Ptl; R_2 = Ph; R_3 = Me
b, R_1 = Ptl; R_2 = R_3 = Ph
c, R_1 = Ptl; R_2 = R_3 = Me
d, R_1 = Ptl; R_2 = Me; R_3 = Ph
(Ptl = phthalimido)

have reported results describing the neat pyrolysis of 2*H*-azirine-2-carboxamides (**14**) and 5-aminoisoxazoles (**15**). The authors suggest that intermediate **17** has diradical character, but a vinyl nitrene would also be consistent with the reaction products. Nishiwaki points out that cleavage of the azirine C–C bond to form intermediate **18** is also a mechanistic possibility (Scheme V).

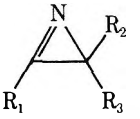
As a result of our interest in bond-breaking phenomena in small ring compounds,[10] we chose to study the thermal decompositions of substituted 2*H*-azirines. The original intent of this work was to elucidate the nature of the intermediate formed upon thermal C–N bond cleavage in 2*H*-azirines. However, the formation of unexpected products indicated that we had uncovered the first clear-cut example of products formed from carbon–carbon bond cleavage as a major pathway in 2*H*-azirine thermal decomposition, leading to formation of iminocarbenes.

Scheme V



Results

In the course of our work, it was necessary to synthesize azirines **19a–d**. Compounds **19a** and **19b** were prepared via



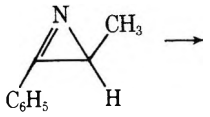
19a, R_1 = Ph; R_2 = Me; R_3 = H
b, R_1 = Ph; R_2 = Et; R_3 = H
c, R_1 = Ph; R_2 = R_3 = Me
d, R_1 = Me; R_2 = Ph; R_3 = Me

the vinyl azide route of Hassner[11a,b] and **19c** and **19d** were synthesized from the appropriate dimethylhydrazone methiodide.[12a,b] These materials were subjected to pyrolysis in a quartz flow system at atmospheric pressure using helium as a carrier gas. Typical residence times in the pyrolysis zone were approximately 10 s. Products were condensed in a double U-tube trap at −196 °C.

Polymerization of some of the pyrolysis products in the collection trap was a troublesome problem in this work. Extensive efforts were made to minimize polymerization; nevertheless 30–40% polymeric material was isolated from every pyrolysis. Even though the yield of polymer varied by as much as 10%, the proportions of apparently nonpolymerizing products remained constant in separate pyrolyses at a given temperature.

Pyrolysis (cf. Chart I) of 2-methyl-3-phenyl-2*H*-azirine (**19a**) at 565 °C consumed all the starting material. The monomeric products formed were styrene (56%) and benzonitrile (2%) (presumably HCN was also formed; vide infra). Fragmentation products of styrene comprised 4% of the pyrolysate and included ethylbenzene, toluene, and benzene. The pyrolysis of **19a** at several lower temperatures was monitored by vapor phase chromatography. No buildup of intermediate products was observed at 320 (0% conversion), 390, 466, or 523 °C.

Chart I. Products of the 565 °C Pyrolysis of 2-Methyl-3-phenyl-2*H*-azirine (19a)

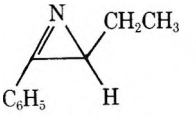


19a

$C_6H_5—CH=CH_2$ (56%) + $C_6H_5—C\equiv N$ (2%) + polymer (38%) + other (4%)

The apparent generality of this unexpected fragmentation for 2-alkyl-3-phenyl-2*H*-azirines was demonstrated by pyrolysis of **19b** at 565 °C (Chart II) ("other" includes

Chart II. Products of the 565 °C Pyrolysis of 2-Ethyl-3-phenyl-2*H*-azirine (19b)



19b

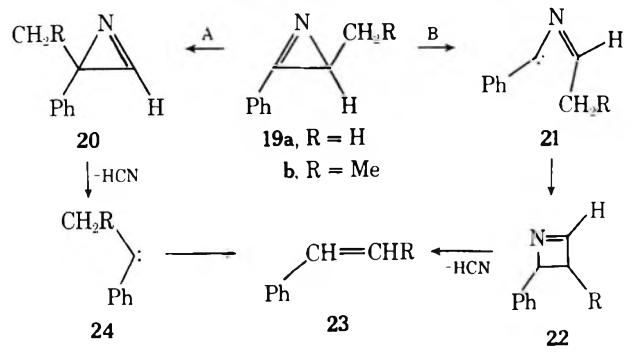
$C_6H_5—CH=CH—CH_3$ (cis and trans 42%) + $C_6H_5—CH=CH_2$ (9%) + $C_6H_5—C\equiv N$ (2%)

polymer (39%) + other (8%)

mainly fragmentation products of β-methylstyrene, i.e., ethylbenzene, toluene, and benzene). *trans*- and *cis*-β-methylstyrene equilibrate thermally at 565 °C; the observed trans:cis ratio of 2:1 is the equilibrium mixture at this temperature.

In order to explain the formation of styrenes from **19a** and **19b**, bonding between C-3 of the azirine ring and the substituent carbon attached to C-2 must occur during the course of reaction. Two possible mechanistic routes which accomplish the observed transformation are shown in Scheme VI; however, neither path seems particularly reasonable as written. In path A, the azirine **20** (which has a hydrogen substituent at the 3 position) would be expected to rapidly decompose under our reaction conditions.[8,13] However, the first step in this mechanism involves an unprecedented 1,3-alkyl shift in an unsaturated ring. Path B involves carbon–carbon bond cleavage and 1,4-carbene insertion into a C–H bond to form azetine **22**.[14] Jones[15] has observed a case in which a carbene does presumably insert to form a four-membered ring; however, hydrogen abstraction would be expected to be a more facile process than C–H insertion in our system. In 1971 Hassner reported that cyclopropyl azides smoothly decompose to azetines and olefinic fragmentation products.[16] He suggested that the olefins could be coming from azetine decomposition, but does not rigorously prove it.

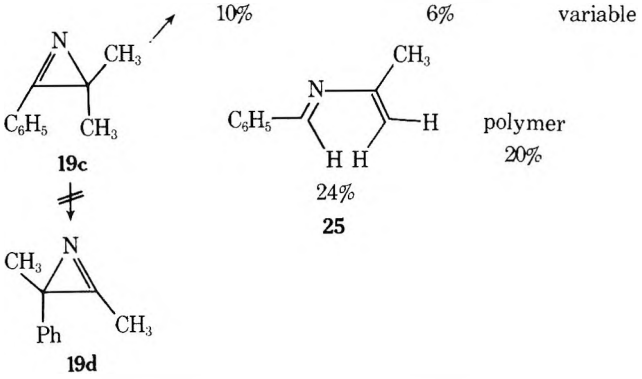
Scheme VI



20 **19a**, R = H, **b**, R = Me **21** **24** **23** **22**

Chart III. Products of the 472 °C Pyrolysis of 2,2-Dimethyl-3-phenyl-2*H*-azirine (19c)

$C_6H_5—CH=CH_2$ (10%) + $C_6H_5—C\equiv N$ (6%) + CH_3CN (variable)



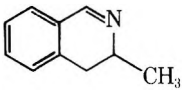
19c **25** (24%) polymer (20%)

19d

Path A is relatively easy to test. Pyrolysis of **19c** should result in formation of **19d** (isolable at partial conversion temperatures) if 1,3-alkyl shifts are important in 2*H*-azirine decomposition. Also, acetonitrile should be the other fragmentation product, analogous to the presumed HCN obtained from decomposition of **19a**.

In analogy with **19a** and **19b**, pyrolysis of **19c** at 472 °C (60% conversion) also gave styrene and benzonitrile (Chart III). *No* methyl-shifted azirine **19d** was observed (nor was its thermal decomposition product; vide infra) but acetonitrile in variable amounts was detected in this case. In addition, a significant new product was obtained in 24% yield; its spectral data were consistent with azabutadiene **25**. In confirmation of this assignment, hydrolysis[17] of **25** in aqueous mineral acid gave benzaldehyde and acetone.

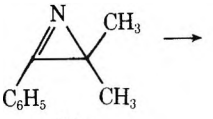
Formation of **25** provided the needed clue to understanding the mechanism of these pyrolyses, since we were able to show that it was converted to styrene under the reaction conditions. At higher temperatures (545 °C), **25** gave a 14:1 ratio of styrene and 3-methyldihydroisoquinoline (**26**). Pyrolysis of the 2*H*-azirine **19c** at 545 °C gave an ~11:1 ratio of styrene and **26** (Chart IV). The similar ratios



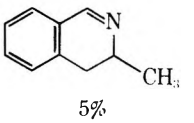
26

of styrene and **26** in the azirine **19c** and azabutadiene (**25**) 545 °C pyrolyses strongly implicate **25** as the major primary pyrolysis product of **19c**.

Chart IV. Products of the 545 °C Pyrolysis of 2,3-Dimethyl-3-phenyl-2*H*-azirine (19c)



19c

$C_6H_5—CH=CH_2$ (56%) + $C_6H_5—C\equiv N$ (4%) +  (5%)

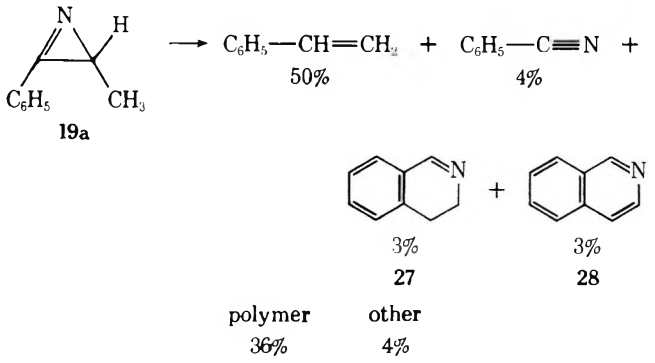
26

polymer (32%) other (3%)

We were unable to isolate an azabutadiene intermediate from the pyrolysis of 2-methyl-3-phenyl-2*H*-azirine (**19a**). Apparently the azabutadiene is involved in the polymerization process, and its rate for polymerizing or fragmentation

to styrene precludes its isolation. Nevertheless, the higher temperature conversion of azabutadiene (**25**) to the new product, dihydroisoquinoline (**26**), provided a possible test for the presence of an azabutadiene in the pyrolysis of **19a**. Since formation of **26** became competitive with fragmentation to styrene at higher temperatures, **19a** was pyrolyzed at 580 °C in anticipation of isolating 3,4-dihydroisoquinoline. Our hopes were realized, as demonstrated in Chart V.

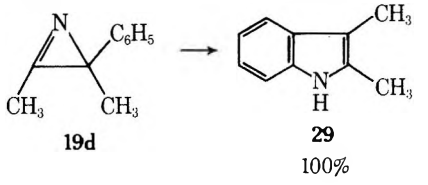
Chart V. Products of the 580 °C Pyrolysis of 2-Methyl-3-phenyl-2*H*-azirine (19a)



The oxidation of dihydroisoquinoline (**27**) to isoquinoline (**28**) at these temperatures is precedented by the high-temperature dihydronaphthalene to naphthalene conversion.[18] Isolation of the dihydroisoquinoline at higher temperatures strongly suggests that **19a** is also isomerizing to an azabutadiene.

The intervention of a competing alkyl-shift isomerization path (path A, Scheme VI) was rigorously ruled out by independent synthesis and pyrolysis of the "alkyl-shifted azirine" **19d** (Chart VI). Quantitative conversion of **19d** to

Chart VI. Products of the 480 °C Pyrolysis of 2,3-Dimethyl-2-phenyl-2*H*-azirine (19d)



the indole **29** is indicative of ring opening to the vinyl nitrene which then inserts into a phenyl C–H bond (Scheme II).

The formation of acetonitrile from **19c** suggests that HCN is, in fact, the small molecule which is extruded during the pyrolysis of **19a** and **19b**. Our inability to isolate acetonitrile in an amount equivalent to styrene (from the **19c** pyrolyses) initially proved disconcerting, especially when control experiments established that acetonitrile could be recovered quantitatively after passing it through the pyrolysis system at 545 °C. However, when a ~5:1 *mixture* of azirine **19c** and acetonitrile was pyrolyzed at 470 °C, *no* acetonitrile was isolated. This more accurate control experiment suggests strongly that acetonitrile is in fact polymerizing under the reaction conditions. Also, the proportion of azabutadiene (**25**) was reduced from 24% (Chart III) to 7% in this pyrolysis; it appears that azabutadiene is also involved in the polymerization.

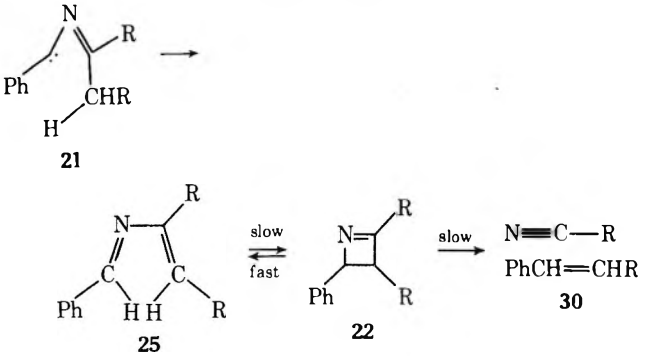
Efforts to retard the polymerization by copyrolysis of **19c** with solvent (and also by trapping the pyrolysate in solvent) were attempted with some success. A tenfold excess of diethyl ether was mixed with azirine **19c** in the vapor phase just outside the oven. The product traps contained an additional threefold excess of frozen diethyl ether prior to pyrolysis. In this manner, acetonitrile was isolated in 55% yield relative to styrene in one pyrolysis at 470 °C. However, these results were not reproducible; recovery of acetonitrile in 10% yield relative to styrene was a more typical result. Control experiments demonstrated the stability of diethyl ether to the reaction conditions.

Discussion

The results outlined above indicate that (1) carbon–carbon bond cleavage occurs upon thermolysis of 3-phenyl-2-alkyl-2*H*-azirines, (2) azabutadienes are primary pyrolysis products and precursors to the fragmentation products (styrenes and presumably nitriles), and (3) the azabutadiene to dihydroisoquinoline rearrangement is a competitive process at higher temperatures. Mechanistic questions which we will try to answer include (1) How do azabutadienes lead to the observed fragmentation products? (2) What is the nature of the species formed upon carbon–carbon bond rupture? (3) Why does this particular family of azirines (**19a–c**) display this behavior? (4) How does dihydroisoquinoline formation from azabutadienes occur?

The detection of azabutadienes as pyrolysis products makes reconsideration of path B in Scheme VI worthwhile. However, rather than postulating C–H insertion by the initially formed[22] carbene **21**, we believe that hydrogen abstraction occurs to form the imine **25** (1,4-hydrogen abstraction by vinyl carbene- or 1,3-diradical-like species, generated from thermal ring opening of substituted cyclopropenes, has ample precedent;[10,19–21] 1,3-butadienes comprise a significant portion of the pyrolysis products of alkyl-substituted cyclopropenes and have been postulated as being formed from vinyl carbene or 1,3-diradical species). An *endothermic* thermal electrocyclization may then generate a small steady state amount of azetine (**22**), which fragments to the observed products (Scheme VII);

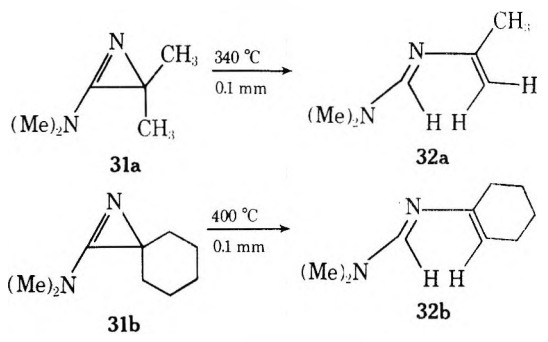
Scheme VII



Aue and Thomas have recently invoked a similar azetine–azabutadiene equilibrium to explain results in the gas-phase pyrolysis of 2-alkoxy-1-azetines.[23a] Additional support for 1,4-hydrogen transfer in iminocarbenes is provided by the very recent work of Ghosez and co-workers.[23b] These workers have shown that 3-amino-2-alkyl-2*H*-azirines **31a** and **31b** appear to be undergoing a similar C–C bond cleavage with subsequent formation of azabutadienes **32a** and **32b** (Scheme VIII). These authors report *no* fragmentation products analogous to the ones we observed, but this may be rationalized by considering that Ghosez' pyrolysis temperatures were 100–200 °C lower than in our work (where fragmentation was significant).[23b]

Our postulated azabutadiene–azetine equilibrium parallels the butadiene–cyclobutene thermal conversion. Brauman and Stephenson[24] have presented strong evidence that butadiene is in equilibrium with a small amount of cyclobutene at 637 °C in the gas phase.

Scheme VIII

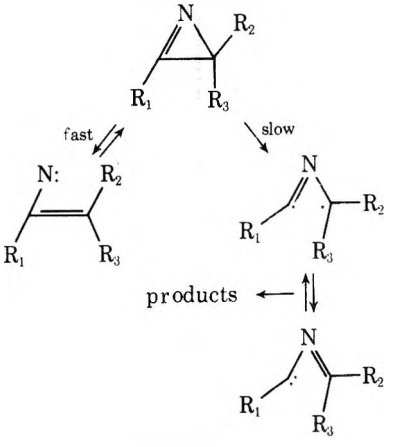


31a 32a

31b 32b

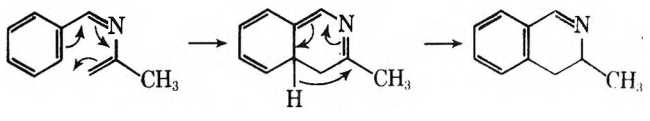
In our system the initial bond-breaking preference (C–N vs. C–C) has not been determined. N(sp^2)–C(sp^3) bonds are probably 5–10 kcal/mol weaker than C(sp^2)–C(sp^3) bonds. This guess is based solely on analogy to sp^3–sp^3 bond dissociation energies[25] in carbon and nitrogen systems; there are no values in the literature for the particular bond strengths in question. For all thermal azirine rearrangements investigated, other than ours and Ghosez',[23] *carbon–nitrogen* bond cleavage to form a vinyl nitrene seems to be the preferred bond-breaking process. It seems reasonable that C–N bond cleavage is also the lowest energy pathway in our system. However, by analogy with the work of Rees[8] (**9c** and **9d**, Scheme IV), the nitrene generated from **19a–c** will not undergo 1,4-hydrogen abstractions. The independent work of Isomura[6,7] and Rees[8] suggests that 1,2 abstraction by the nitrene (to form ketenimines) only occurs when hydrogen is the group being transferred. Consequently it is reasonable that no product-formation path, other than regeneration of the azirine, is available to the nitrene. Thus, reaction products are observed only when pyrolysis temperatures high enough to cause C–C cleavage are reached (Scheme IX). A test of this hypothesis awaits a more sophisticated experiment, such as the thermal racemization[10] of an optically active azirine.

Scheme IX



The conversion of azabutadiene (**25**) to dihydroisoquinoline (**26**) is a novel transformation in its own right. The first step of this process can be viewed as an electrocyclic ring closure of an azahexatriene to a 1,3-azacyclohexadiene. The second step simply involves a symmetry allowed, 1,5-suprafacial sigmatropic hydrogen migration (Scheme X). Weber and co-workers have recently observed the all-carbon analogue of this rearrangement; i.e., the conversion of phenyl-1,3-butadiene to dihydronapthalene.[26]

Scheme X



Experimental Section

A. Synthesis of Starting Azirines. 2-Ethyl-3-phenyl-2*H*-azirine (19b). Compound **19a** was prepared by photolysis of the corresponding azoalkene as described by Hassner,[11] and the same procedure was then applied to the synthesis of **19b**. After the solvent was removed by rotary evaporation, the azirine **19b** was vacuum transferred and purified by preparative VPC on column A (130 °C, 100 ml/min): ir 3090, 3060, 2980, 2960, 2900, 1746, 1615, 1508, 1480, 1470, 1395, 1340, 1321, 1165, 1088, 1045, 1003, 940, 910, 895, 705 cm^{-1}; NMR (CCl_4) δ 0.92 (t, 3 H, $-CH_2CH_3$), 1.35–1.90 (m, 2 H, $-CH_2CH_3$), 2.13 (t, 1 H, $>CHCH_2$), 7.38–8.00 (m, 5 H, phenyl).

2,3-Dimethyl-2-phenyl-2*H*-azirine (19d). Compound **19c** was prepared as described by Leonard,[12] and the method was then extended to the synthesis of **19d** (starting with 3-phenyl-2-butanone). This azirine was obtained in 30% yield and was purified by preparative VPC on column A (130 °C, 100 ml/min): ir 3050, 2980, 2960, 2890, 1775, 1615, 1510, 1460, 1445, 1392, 1380, 1279, 1082, 1045, 823, 710 cm^{-1}; NMR (CCl_4) δ 1.60 (s, 3 H, (Ph)C–CH_3), 2.34 [s, 3 H, –(CN)CH_3], 6.90–7.50 (m, 5 H, phenyl); high-resolution mass calcd, 145.089145; high-resolution mass observed, 145.0888.

B. Vapor Phase Chromatographic Analysis. All analytical vapor phase chromatography was performed on a Hewlett-Packard 5750 research chromatograph equipped with a Hewlett-Packard 3370A digital integrator. The chromatograph was equipped with a flame ionization detector. Preparative vapor phase chromatography was performed on a Varian Aerograph 90-P3 chromatograph equipped with a thermal conductivity detector. The following columns were used: column A, 10 ft × 0.375 in., 20% UCW-98, on 60/80 Chromosorb WAW-DMCS, glass; column B, 10 ft × 0.25 in., 10% DEGS on 60/80 Chromosorb P-NAW, glass; column C, 10 ft × 0.25 in., 30% SE-30 on 60/80 Chromosorb WAW-DMCS, glass; column D, 8 ft × 0.125 in., 10% SE-30 on 100/120 Chromosorb WAW-DMCS, aluminum; column E, 12 ft × 0.125 in., 15% DEGS on 100/120 Chromosorb WAW-DMCS, aluminum.

C. Pyrolyses. Flow pyrolyses were carried out utilizing a 1.2 cm o.d. quartz tube flow system contained in a Hoskin's tube furnace. Auxiliary heating wires, wrapped with asbestos tape, prevented sample condensation in the flow system at both the inlet and outlet sides. The pyrolysis products were collected in a double U-tube trap filled with Pyrex helices and maintained at −196 °C. Drying towers attached to the traps prevented condensation of moisture in the traps. The temperature of the quartz tube was monitored by an iron–constantan thermocouple. The neat reactants were introduced into the pyrolysis zone by a flow of helium (200 ml/min).

In a typical pyrolysis, 50–500 mg of VPC-purified starting material was carried through the reaction zone over the course of several hours. The pyrolysate was immediately taken up in diethyl ether to minimize polymerization in the collection traps.

Initial pyrolyses were carried out at a temperature where a given azirine was just quantitatively consumed. At these temperatures (typically 500–600 °C) monomeric product accounted for 55–65% of the pyrolysate. A reddish polymeric material comprised the remainder of the pyrolysate. Mass balance experiments confirmed that all starting material is accounted for by the trapped monomers and polymer. Relative flame ionization detector sensitivities were determined for all pyrolysis products by analysis of a solution containing known amounts of the products.

The possibility of materials reacting on the surface of the flow system was ruled out by performing a packed-tube pyrolysis. The quartz tube was packed with 1 × 0.2 cm o.d. pieces of quartz tubing. Comparison of open- and packed-tube pyrolyses showed no surface-enhanced reactions to be occurring.

1-Phenyl-3-methyl-2-aza-1,3-butadiene (25). **25** was isolated from a concentrated diethyl ether solution of the 472 °C flow pyrolysis products of **19c** by preparative VPC on column B (100°, 80 ml/min): ir 3040, 3005, 2950, 2900, 2850, 1642, 1616, 1571, 1488, 1447, 1360, 1304, 1257, 1205, 1165, 967, 950, 870, 845, 711, 682 cm^{-1}; NMR (CCl_4) δ 2.00 (s, 3 H, vinyl $-CH_3$), 4.48 (s, 1 H, vinyl H), 4.69 (s, 1 H, vinyl H), 7.30–8.90 (m, 5 H, phenyl), 8.18 (s, 1 H, imino H). Anal. Calcd for $C_{10}H_{11}N$: C, 82.76; H, 7.59; N, 9.66. Found: C, 82.42; H, 7.74; N, 9.84.

The structure of **25** was proved by hydrolysis[17] of a solution of 0.010 g of **25** in 0.100 g of 2-butanone with 1.250 ml of a 10% aqueous HCl solution. The reaction mixture was stirred for 48 h at room temperature. Work-up involved neutralizing with aqueous Na_2CO_3 and extraction into ether. Rigorous spiking experiments on two analytical VPC columns [columns D and E (various tem-

peratures, 80–115 °C, 30 ml/min)] showed the hydrolysis products to have VPC retention times identical with those of authentic samples of benzaldehyde and acetone. The later eluting product was isolated from the hydrolysis extracts by preparative VPC on column B (70 °C and 70 ml/min). This compound's ir spectrum correlated exactly with that of an authentic sample of benzaldehyde.

2,3-Dimethylindole (29). The indole was isolated by preparative VPC from an ether solution of the 480 °C pyrolysate of **19d**. The ir spectrum correlated exactly with ir spectrum 911G, Aldrich Library, for 2,3-dimethylindole: ir 3492, 3060, 2940, 2880, 1625, 1550, 1476, 1346, 1310, 1270, 1253, 1010, 932, 730 cm^{-1}; NMR (CCl_4) δ 2.19 (s, 3 H, 3-CH_3), 2.32 (s, 3 H, 2-CH_3), 6.50–6.85 (broad, 1 H, NH), 6.90–7.45 (m, 4 H, phenyl).

3,4-Dihydroisoquinoline (27). This compound was isolated by preparative VPC of the 580 °C pyrolysate of **19a** on column C (100 °C, 100 ml/min); ir 3100, 3040, 2970, 2920, 2878, 1626, 1576, 1484, 1452, 1443, 1426, 1294, 1272, 1204, 1188, 1113, 1051, 1029, 1000, 951, 918, 873, 857, 683 cm^{-1}; NMR (CCl_4) δ 2.67 (t, J = 7.1 Hz, 2 H, NCH_2CH_2), 3.73 (t of d, J = 7.1, 2.1 Hz, 2 H, NCH_2CH_2), 6.95–7.42 (m, 4, aromatic), 8.17 (t, J = 2.1 Hz, 1 H, imino H). The structure proof was confirmed by oxidation at 530 °C over Pd/C in a quartz flow system. Oxidized product spectra correlated exactly with those of authentic isoquinoline.

Isoquinoline (28). The 580 °C pyrolysis of **19a** produces isoquinoline, presumably from oxidation of 3,4-dihydroisoquinoline.[18] This pyrolysis product was isolated by preparative VPC of a concentrated ether solution of the pyrolysate (column C, 100 °C, 100 ml/min): ir 3080, 3002, 2987, 1628, 1589, 1574, 1505, 1382, 1375, 1270, 1247, 1213, 1136, 1033, 1011, 941, 853, 816 cm^{-1}; NMR (CCl_4) δ 6.90–8.2 (m, 6 H), 5.58 (d, 1 H), 6.29 (s, 1 H). The spectral data correlated exactly with the spectra of an authentic sample of isoquinoline.

3,4-Dihydro-3-methylisoquinoline (26). **26** was isolated from a concentrated ether solution of **19c** by preparative VPC on column C (100 °C, 100 ml/min): ir 3078, 3040, 2980, 2943, 2897, 2840, 1670, 1585, 1500, 1468, 1439, 1390, 1368, 1327, 1304, 1227, 1211, 1141, 1130, 1058, 1043, 960, 943, 930, 898, 820, 709 cm^{-1}; NMR (CCl_4) δ 1.31 (d, J = 6.8 Hz, 3 H, -CH_3), 2.68 (d, J = 4.0 Hz, 2 H, CH_3CHCH_2–), 3.32–4.90 (m, 1 H, -$CHCH_3$), 6.90–7.40 (m, 4 H, aromatic), 8.18 (d, J = 2.2 Hz, 1 H, imino H); mass spectrum M^+ m/e 145, 144, 130, 117, 103, 90, 76, 77, 51, 27. This dihydroisoquinoline was oxidized in the same manner as described for 3,4-dihydroisoquinoline (**27**). In the course of oxidation, the methyl group was cleaved, and isoquinoline was obtained.

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Registry No.—**19a**, 16205-14-4; **19b**, 51209-52-0; **19c**, 14491-02-2; **19d**, 57573-53-2; **25**, 51209-53-1; **26**, 14123-78-5; **27**, 3230-65-7; **28**, 119-65-3; **29**, 91-55-4.

References and Notes

(1) A preliminary account of this work has been published. L. A. Wendling and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 308 (1974).
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A Convenient Two-Step Synthesis of 4-(2-Imidazolyl)phthalazones from o-Phthaloyl Dichloride

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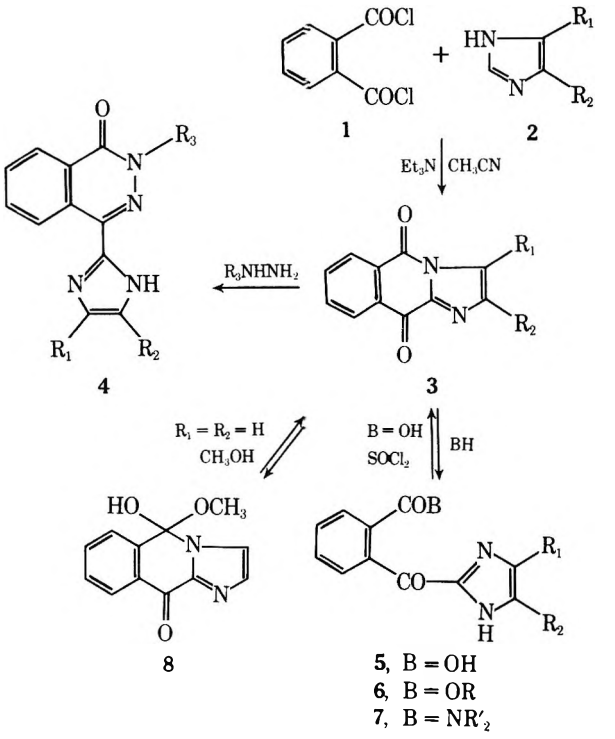
The imidazo[1,2-*b*]isoquinoline-5,10-diones (**3**) derived from the condensation of equimolar amounts of *o*-phthaloyl dichloride (**1**) and an imidazole (**2**) in the presence of 2 molar equiv of Et_3N, react readily with hydrazines R_3NHNH_2 (R_3 = H, alkyl, aryl) to form 4-(2-imidazolyl)phthalazones (**4**), a new class of compounds. The reactions of these carbonyl reagents differ from those of nucleophiles such as hydroxide ion, alcohols, and amines which attack **3** at the lactam carbonyl group and form the carboxylic acid derivatives (**5**–**7**).

The patent literature[1,2] describes the condensation of equimolar amounts of *o*-phthaloyl dichloride (**1**) and imidazoles or benzimidazoles (**2**) possessing unsubstituted 1 and 2 positions in CH_3CN containing 2 molar equiv of Et_3N to produce imidazo[1,2-*b*]isoquinoline-5,10-diones (**3**), which react with nucleophiles such as hydroxide ion,

Scheme I



alcohols, and amines at the lactam carbonyl group to form the corresponding carboxylic acids (**5**), esters (**6**), and amides (**7**) (Scheme I). We have verified these observations, and have included a few representative examples of structures **3** and **5–7** in the Experimental Section to illustrate their spectral characteristics, which were not described in the Bayer patents. We have also shown structure **3** (R_1 + R_2 = CH=CHCH=CH) to be identical with the CrO_3 oxidation product of α-(2-benzimidazolyl)-o-toluic acid[3] by mixture melting point and spectra.

The reaction products of **3** with carbonyl reagents have not been previously described, and we have discovered a convenient two-step synthesis of the new 4-(2-imidazolyl)phthalazones (**4**) from **1** as a consequence of this work. Reactive difunctional carbonyl reagents such as hydrazine and its monosubstituted analogues (R_3 = CH_3, C_6H_5) attack both the ketonic and lactam carbonyl groups of **3** to form the new heterocyclic ring in **4** and leave the imidazole moiety as a pendant group. This reaction has some similarities to our recent synthesis of 2-aryl-3,3a-dihydro-8*H*-pyrazolo[5,1-*a*]isoindol-8-ones from 3-phenacylphthalides[4] where hydrazine attacks both a ketonic and a lactone carbonyl group to form a new heterocyclic ring.

A few comments are in order concerning the interconversions of structures **3** and **5–7**, which are not evident from the Bayer work. We have found that the carboxylic acid **5** (R_1 = C_6H_5; R_2 = H) is readily cyclized to **3** (R_1 = C_6H_5; R_2 = H) with excess $SOCl_2$. Ring opening of the imidazo[1,2-*b*]isoquinoline-5,10-diones (**3**) with alcohols does not occur as readily as that of the more strained 2-aryl-8*H*-pyrazolo[5,1-*a*]isoindol-8-ones which we recently described.[4,5] The latter compounds have some structural similarity to **3**. Attempts to cleave **3** (R_1 = R_2 = H) with MeOH containing traces of methoxide at 25° produced recovered **3** on evaporation.[5] However, the uv spectrum of **3** in DMF differs from that in MeOH, indicating that the first step in the methanolysis is formation of structure **8**. Unless considerable amounts of acid or base are present, **8** reverts to **3**. More vigorous conditions, such as refluxing the alcoholic solvent containing **3** and molar amounts of base[2] or mineral acid, are required to convert **3** to **6**.

Experimental Section[6]

Imidazo[1,2-*b*]isoquinoline-5,10-dione (**3**, R_1 = R_2 = H) was prepared from **1** and imidazole according to the literature[1] in 32% yield (0.1 mol scale) after recrystallization (DMF). The crude product is a green powder, but after repeated recrystallization it forms yellow prisms with mp 238–239 °C dec (lit.[1] mp 236 °C); ν_{max} 1720, 1670, and 1580 cm^{-1}; λ_{max} (DMF) 365 nm (ε 2040) and 322 (3980); ^1H NMR (Me_2SO-d_6) δ 8.33–7.85 (m) 5 H and 7.48 ppm (d, J = 2 Hz) 1 H. Anal. Calcd for $C_{11}H_6N_2O_2$: C, 66.66; H, 3.05; N, 14.14. Found: C, 67.42; H, 3.05; N, 14.25.

2(3)-Phenylimidazo[1,2-*b*]isoquinoline-5,10-dione[7] (**3**, R_1 = C_6H_5; R_2 = H) was prepared similarly from **1** and 4-phenylimidazole (Aldrich) in 32–49% crude yield as a green powder. Recrystallization (DMF) gave pure material as olive-bronze crystals with mp 285–288 °C dec; ν_{max} 1715 and 1670 cm^{-1}; λ_{max} (DMF) 402 nm (ε 2400) and 274 (23 800); ^1H NMR ($CDCl_3$) δ 8.58–8.37 (m) and 8.20–7.88 (m) 4 H, 7.67 (m) 4 H, 7.53 (m) and 7.40 ppm (m) 2 H. Anal. Calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.68; N, 10.21. Found: C, 74.19; H, 3.82; N, 10.26.

Benzimidazo[1,2-*b*]isoquinoline-5,12-dione (**3**, R_1 + R_2 = CH=CHCH=CH) was prepared similarly from **1** and benzimidazole in 64% yield after recrystallization (DMF). The pure material was a yellow, crystalline solid with mp 268–271 °C dec (lit.[1,3] 270, 261–262 °C); ν_{max} 1710 and 1670 cm^{-1}; λ_{max} (DMF) 418 nm (ε 2170) and 283 (20 600); ^1H NMR (CF_3CO_2H) δ 8.33–7.88 (m) 3 H and 7.67–7.45 ppm (m) 5 H. Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.57; H, 3.25; N, 11.29. Found: C, 72.46; H, 3.37; N, 11.28.

4-(2-Imidazolyl)phthalazone (**4**, R_1 = R_2 = R_3 = H). A mixture of **3** (R_1 = R_2 = H) (10.0 g, 50.5 mmol), EtOH (100 ml), and hydrazine hydrate (5.0 g, 0.10 mol) was stirred at reflux for 3 h and cooled to 0 °C, and the crystalline product was filtered. Recrystallization (DMF) gave an 87% yield of colorless, crystalline phthalazone with mp >300 °C; ν_{max} 3420 and 1650 cm^{-1}; λ_{max} (CF_3CO_2H) 310 nm (ε 6700), 300 (9600), and 292 nm (10 200); ^1H NMR (CF_3CO_2H) δ 8.77–8.00 (m) 4 H (C_6H_4) and 8.03 ppm (s) 2 H (CH=CH). Anal. Calcd for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; *m/e* 212.0698. Found: C, 62.20; H, 3.70; *m/e* 212.0695.

2-Methyl-4-(2-imidazolyl)phthalazone (**4**, R_1 = R_2 = H; R_3 = CH_3) was prepared similarly from **3** (R_1 = R_2 = H) and methylhydrazine in 55% yield after recrystallization (CH_3CN). It formed colorless crystals with mp 241–242 °C; ν_{max} 1660 cm^{-1}; λ_{max} (CF_3CO_2H) 313 nm (ε 10 400) and 302 (12 000); ^1H NMR (CF_3CO_2H) δ 8.65–7.90 (m) 4 H (C_6H_4), 7.57 (s) 2 H (CH=CH), and 4.07 ppm (s) 3 H (NCH_3). Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; *m/e* 226.0854. Found: C, 63.72; H, 4.28; *m/e* 226.0814.

2-Phenyl-4-(2-imidazolyl)phthalazone (**4**, R_1 = R_2 = H; R_3 = C_6H_5) was prepared similarly in aqueous HOAc from **3** (R_1 = R_2 = H) and phenylhydrazine in 60% yield after recrystallization (50% DMF). It formed orange crystals with mp 210–211 °C; ν_{max} 3340, 3210, and 1700 cm^{-1}; λ_{max} (DMF) 443 nm (ε 1910) and 284 (3250); ^1H NMR (CF_3CO_2H) δ 8.58–7.58 (m) 4 H (C_6H_4), 7.43 (s) 2 H (CH=CH), and 7.22 ppm (s) 5 H (C_6H_5). Anal. Calcd for $C_{17}H_{12}N_4O{\cdot}H_2O$: C, 66.65; H, 4.61; N, 18.29. Found: C, 67.37; H, 4.84; N, 18.65.

2-Methyl-4-(4-phenyl-2-imidazolyl)phthalazone (**4**, R_1 = C_6H_5, R_2 = H, R_3 = CH_3) was prepared similarly from **3** (R_1 = C_6H_5, R_2 = H) and methylhydrazine in 45% yield after recrystallization (80% DMF). It formed yellow crystals with mp 307 °C dec; ν_{max} 3400, 3250, and 1630 cm^{-1}; λ_{max} (DMF) 413 nm (ε 2380) and 339 (12 000); ^1H NMR (Me_2SO-d_6) δ 12.82 (broad) 1 H (NH), 9.75–7.25 (m) 10 H (aromatic), and 3.83 ppm (s) 3 H (NCH_3). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.52; H, 4.54; N, 18.98.

4-(2-Benzimidazolyl)phthalazone (**4**, R_1 + R_2 = CH=CHCH=CH; R_3 = H) was prepared similarly from **3** (R_1 + R_2 = CH=CHCH=CH) and hydrazine hydrate in 87% yield after recrystallization (75% DMF). It formed colorless crystals with mp >315 °C; ν_{max} 3220 and 1660 cm^{-1}; λ_{max} (DMF) 324 nm (ε 18 000) and 281 (14 100); ^1H NMR (CF_3CO_2H) δ 8.33–8.12 (m) 1 H and 7.73–7.17 (m) 7 H. Anal. Calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.79; H, 3.87; N, 21.12.

2-Methyl-4-(2-benzimidazolyl)phthalazone (**4**, R_1 + R_2 = CH=CHCH=CH; R_3 = CH_3) was prepared similarly from **3** (R_1 + R_2 = CH=CHCH=CH) and methylhydrazine in 81% yield after recrystallization (45% DMF). It formed yellow crystals with mp 253–255 °C; ν_{max} 3290 and 1630 cm^{-1}; λ_{max} (DMF) 401 nm (ε 830), 332 (17 700), and 281 (14 100); ^1H NMR (CF_3CO_2H) δ 8.30–8.10 (m) 1 H, 7.72–7.22 (m) 7 H, and 3.67 ppm (s) 3 H (NCH_3). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38. Found: C, 69.39; H, 4.32.

2-(2-Carboxybenzoyl)imidazole (5, $R_1 = R_2 = H$). A mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29 mmol), H_2O (30 ml), MeOH (30 ml), and NaOH (2.0 g, 50 mmol) was stirred at 25 °C for 2 h. Neutralization of the resulting solution (pH 7) gave a colorless precipitate which was recrystallized (210 ml of MeOH) to give 4.31 g (20 mmol, 69%) of product as colorless needles with mp 228–229 °C dec (lit.[2] 200 °C); ν_{max} (Nujol) 3290 and 1670 cm^{-1}; λ_{max} (MeOH) 287 nm (ϵ 13 300); ^1H NMR (Me_2SO-d_6) δ 12.17 (broad) 2 H (CO_2H, NH), 8.03–7.80 (m) and 7.67–7.53 (m) 4 H (C_6H_4), and 7.27 ppm (s) 2 H (CH=CH). Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.17; H, 3.75; N, 13.23.

2-(2-Carboxybenzoyl)-4-phenylimidazole[7] (5, $R_1 = C_6H_5$, $R_2 = H$) was prepared similarly from 3 ($R_1 = C_6H_5$; $R_2 = H$) in 82% yield after recrystallization from a mixture of MeOH (20 ml), Me_2SO (10 ml), and H_2O (2 ml). The product was a colorless solid with mp 280 °C dec; ν_{max} (Nujol) 3350 and 1670 cm^{-1}; λ_{max} (MeOH) 323 nm (ϵ 16 300) and 250 (12 700); ^1H NMR (Me_2SO-d_6) δ 8.00–7.58 (m) 7 H and 7.47–7.17 ppm (m) 3 H. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.54; H, 4.23; N, 9.32.

2-(2-Carboxybenzoyl)benzimidazole (5, $R_1 + R_2$ = CH=CHCH=CH) was prepared similarly from 3 ($R_1 + R_2$ = CH=CHCH=CH) in 92% yield after recrystallization (67% MeOH). The product was a colorless solid with mp 270–271 °C (lit.[2] 250 °C); ν_{max} 3380, 3320, and 1680 cm^{-1}; λ_{max} (MeOH) 310 nm (ϵ 15 300) and 240 (10 200); ^1H NMR (Me_2SO-d_6) δ 13.40 (broad) 2 H (CO_2H, NH) and 8.12–7.17 ppm (m) 8 H (aromatic). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 65.86; H, 3.70; N, 10.23.

Cyclization of 2-(2-Carboxybenzoyl)-4-phenylimidazole. A mixture of 5 ($R_1 = C_6H_5$; $R_2 = H$) (1.0 g, 3.45 mmol) and $SOCl_2$ (20 ml) was warmed on a steam bath for 5 min, then evaporated to leave 0.8151 g (2.98 mmol, 87%) of 2(3)-phenylimidazo[1,2-*b*]isoquinoline-5,10-dione (3, $R_1 = C_6H_5$; $R_2 = H$) as a yellow solid, mp 288–290.5 °C. Recrystallized material (DMF) was identical spectrally with material prepared from 1 and 2 ($R_1 = C_6H_5$; $R_2 = H$) above.

Treatment of 3 ($R_1 = R_2 = H$) with MeOH. A mixture of 3 ($R_1 = R_2 = H$) (1.0 g, 5.05 mmol), MeOH (20 ml), and a small chip of sodium was stirred at 25 °C for 1.5 h. The yellow color faded and the dione went into solution, but isolation by evaporation gave only starting material. Comparison of the uv spectra of 3 ($R_1 = R_2 = H$) in DMF [λ_{max} 365 nm (ϵ 2040) and 322 (3980)], where no reaction can occur, and in MeOH [λ_{max} 290 nm (ϵ 14 200)] with an authentic sample of ester 6 ($R_1 = R_2 = H$; R = C_2H_5) [λ_{max} (EtOH) 290 nm (ϵ 13 100)] suggests the presence of species 8 in methanol solutions of 3; 8 reverts to 3 on isolation.

2-(2-Carboethoxybenzoyl)imidazole (6, $R_1 = R_2 = H$; R = C_2H_5) was prepared by stirring a mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29.0 mmol), EtOH (50 ml), and H_2SO_4 (2 ml) at reflux for 2 h, during which time the solid dissolved. The mixture was diluted (H_2O) and neutralized (pH 7) to give 8 as a colorless precipitate, yield 4.97 g (20.4 mmol, 70%) after recrystallization (160 ml of 25% EtOH). Pure 6 had mp 156–158 °C (lit.[2] 170 °C); ν_{max} 1700, 1600, and 1270 cm^{-1}; λ_{max} (EtOH) 290 nm (ϵ 13 100) and 214 (13 800); ^1H NMR ($CDCl_3$) δ 11.67 (broad) 1 H (NH), 8.42–7.77 (m) 4 H (C_6H_4), 7.18 (s) 2 H (CH=CH), 4.12 (q, J = 7 Hz) 2 H (OCH_2), and 1.07 ppm (t, J = 7 Hz) 3 H (CH_3). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.81; H, 4.80; N, 11.84.

2-(2-Carbamoylbenzoyl)imidazole (7, $R_1 = R_2 = R' = H$). A mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29 mmol) and liquid NH_3 (100 ml) was stirred at −33 °C for 1 h. The solid dissolved to form a colorless solution, evaporation of which gave the crude amide. Recrystallization from a mixture of MeOH (90 ml), Me_2SO (70 ml), and H_2O (150 ml) gave 4.59 g (21.4 mmol, 74%) of colorless, crystalline product with mp 193–194 °C dec; ν_{max} (Nujol) 3290 and 1675 cm^{-1}; λ_{max} (MeOH) 275 nm (ϵ 1265); ^1H NMR (Me_2SO-d_6) δ 12.22 (broad) 1 H (NH), 9.13 and 7.12 (broad) 2 H (NH_2), 7.82–7.42 (m) 4 H (C_6H_4), and 6.92 ppm (s) 2 H (CH=CH). Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22. Found: C, 61.11; H, 4.28.

Registry No.—1, 88-95-9; 2 ($R_1 = C_6H_5$; $R_2 = H$), 670-95-1; 2 ($R_1 + R_2$ = CH=CHCH=CH), 51-17-2; 3 ($R_1 = R_2 = H$), 36142-27-5; 3 ($R_1 = C_6H_5$; $R_2 = H$), 57594-19-1; 3 ($R_1 + R_2$ = CH=CHCH=CH), 6659-72-9; 4 ($R_1 = R_2 = R_3 = H$), 57594-20-4; 4 ($R_1 = R_2 = H$; $R_3 = CH_3$), 57594-21-5; 4 ($R_1 = R_2 = H$; $R_3 = C_6H_5$), 57594-22-6; 4 ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$), 57594-23-7; 4 ($R_1 + R_2$ = CH=CHCH=CH; $R_3 = H$), 57594-24-8; 4' ($R_1 + R_2$ = CH=CHCH=CH; $R_3 = CH_3$), 57594-25-9; 5 ($R_1 = R_2 = H$), 41200-40-2; 5 ($R_1 = C_6H_5$; $R_2 = H$), 57594-26-0; 5 ($R_1 + R_2$ = CH=CHCH=CH), 41200-57-1; 6 ($R_1 = R_2 = H$; $R_2 = C_2H_5$), 41200-53-7; 7 ($R_1 = R_2 = R' = H$), 57594-27-1; 8, 57594-28-2; methylhydrazine, 60-34-4; phenylhydrazine, 100-63-0; hydrazine hydrate, 10217-52-4.

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(7) These compounds are not described in ref 1 and 2.

The Mechanism of Bromination of 4(3*H*)-Quinazolinone, Its 3-Methyl and Its 1,3-Dimethyl Derivatives in Aqueous Acidic Solutions

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The kinetics of bromination of 4(3*H*)-quinazolinone, 3-methyl-4-quinazolinone, and 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate have been measured in dilute aqueous acid media. The kinetic order of the reactions, the acidity dependence of the rates, the inverse dependence of the rates on bromide ion, and the relative reactivities of the substrates are all consistent with a mechanism in which the rate-determining step is attack by molecular bromine upon the covalent hydrate (or pseudobase) of the substrates.

Relatively little has been done on the mechanistics aspects of quinazoline chemistry, although many derivatives have been prepared for potential medicinal purposes.[1] It is known,[2] however, that several simple quinazolines show appreciable covalent hydration,[2,3] particularly in their protonated forms. In aqueous solution 2(1*H*)-quinazolinone[4] exists to the extent of 25% as the covalent hydrate formed by addition of water across the C_4–N_3 double bond,[5] but there is no direct evidence for the covalent hydration of 4(3*H*)-quinazoline (1, R = H). However, it is interesting to

note that the oxidation of **1** (R = H) to 2,4(1*H*,3*H*)-quinazolinedione[6] may occur via its covalent hydrate **3** (R = R′ = H).

Earlier work on 2(1*H*)-pyrimidinones[7] and 4(3*H*)-pyrimidinones[8] has pointed to the involvement of covalent hydrates in the hydrogen–deuterium exchange[7a,8a] reactions and the brominations[7b,8b,c] of these substrates in aqueous media. The object of the present work was to study the bromination of 4(3*H*)-quinazolinone (**1**, R = H) and to ascertain the involvement, or otherwise, of its covalent hydrate **3** (R = R′ = H) in this reaction.

Such studies may have ramifications with respect to oxidations catalyzed by the enzyme xanthine oxidase, e.g., aldehydes to acids, purines to hydroxypurines, and pteridines to hydroxypteridines,[9] since it is a reasonable hypothesis that covalent hydrates are involved in these oxidations. Various heterocyclic systems which are known to undergo covalent hydration are easily oxidized to hydroxy derivatives.[3]

Results and Discussion

Bogert and Geiger[10] reported that attempts to brominate **1** (R = H) with bromine in aqueous potassium bromide solution, in glacial acetic acid, or in acetic anhydride all failed. However, they did obtain a monobromo product by carrying out the bromination in sulfuric acid, but the position of the bromine in their product was not specified.

Contrary to their report[10] we find that **1** (R = H) can be synthetically brominated by bromine in aqueous potassium bromide solution and the 6-bromo product **7** (R = H) can be isolated in high yield. The product so obtained was identical with material made by cyclization of 5-bromoanthranilic acid.[11] Similarly synthetic brominations of **1** (R = Me) and **2** (R = R′ = Me) perchlorate in aqueous methanol gave good yields of **7** (R = Me) and **6** (R = R′ = Me) perchlorate, respectively.

Spectral changes occurring during a bromination of **1** (R = H) carried out in dilute acid (0.01 N H_2SO_4, pH 2.23) were completely consistent with the simple conversion of **1** (R = H) → **7** (R = H). Uv spectra traced at various times after mixing equimolar quantities (4.5×10^{-5} M) of **1** (R = H) and bromine showed a gradual diminution in absorbance due to these substrates, a clean isosbestic point at 304 nm, and a final spectrum identical with that of an authentic sample of **7** (R = H) of the appropriate concentration in the same medium. In neither the synthetic work nor in spectral studies was there any evidence of the formation of any 8-bromo-4(3*H*)-quinazolinone (**8**).[12]

Scheme I

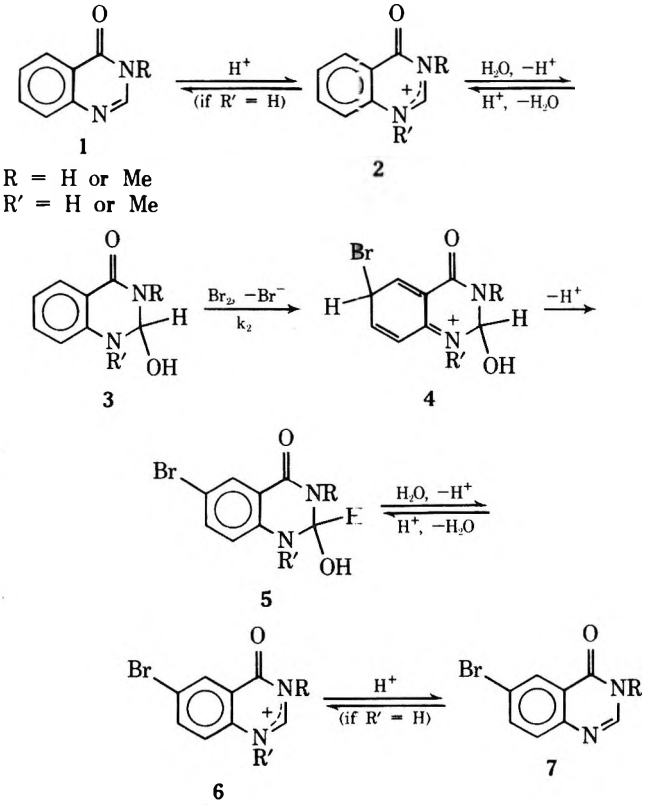
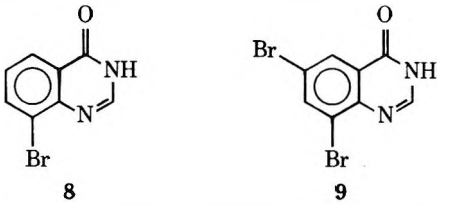


Table I. Variation of Rate of Bromination of 4(3*H*)-Quinazolinone (1, R = H) with Substrate Concentration[a]

[1] × 10^3, M	[Br_2] × 10^4, M	$k_1 \times 10^3$, min^{-1}	Av $k_1 \times 10^3$, min^{-1}
5.0	4.91	114	
	6.51	115	115
4.0	4.94	93.7	
	5.20	94.3	94
2.5	2.27	56.0	
	2.91	56.5	56.3
1.25	1.22	28.4	
	1.33	30.9	29.7

[a] At 30 °C, [KBr] = 0.01 M, acetate buffer pH 3.97. These data are plotted in Figure 1.



We also ruled out the formation of the 6,8-dibromo derivative (**9**) during the bromination of **1** (R = H). It was found that the apparent rate of the bromination **7** (R = H) → **9** is very much slower than that of the parent **1** → **7** (R = H). At 30 °C, **7** (R = H) did not decolorize an equivalent amount of bromine even after 4 days. An attempted synthetic scale dibromination of **1** (R = H) (10 h at 85 °C) was unsuccessful with only the 6-bromo derivative (**7**, R = H) being obtained. However, **9** was obtained by prolonged heating of **7** (R = H) and bromine for 1 week at 50 °C. From these observations the possibility of significant dibromination of **1** (R = H) during the course of the kinetic studies can be safely eliminated, particularly since these were carried out with a tenfold excess of substrate over bromine.

Order of Reaction. Initial titration kinetics suggested a second-order reaction: first order in substrate, and first order in bromine. For convenience, therefore, subsequent kinetics were measured under pseudo-first-order conditions, with an approximate tenfold excess of substrate over bromine. Rate constants (k_1) thus obtained were for the pseudo-first-order disappearance of bromine due to the reaction **1** → **7** (or **2** → **6**).

That this reaction is truly second order is shown by the data in Table I (plotted in Figure 1). The pseudo-first-order rate constants (k_1) diminish linearly with the substrate concentration, and within experimental error, the least-squares line in Figure 1 goes through the origin.[13]

Bromide Ion Dependence. Brominations of the type under consideration produce bromide ion, and thus complex kinetics may be observed since there is a progressive reduction in the concentration of free bromine owing to the formation of tribromide ion.[14] Moreover, there are examples known where tribromide ion acts as an electrophile and gives rise to 1–3% of the product.[15]

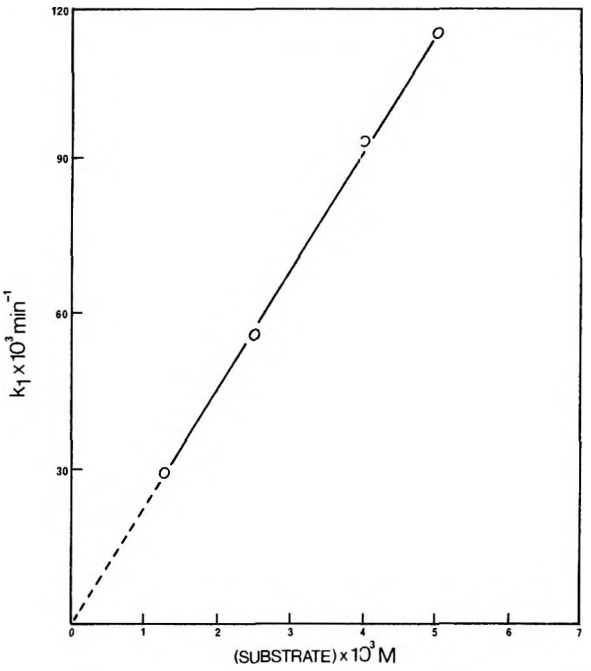


Figure 1. Variation of the rate of bromination of 4(3*H*)-quinazolinone (1, R = H) with substrate concentration.

To swamp the effect of bromide ion produced during kinetic runs all solutions used contained about a 20-fold excess of potassium bromide. In order to see if molecular bromine is the sole brominating agent, or if tribromide ion also makes a contribution,[16] the variation of rate with bromide ion concentration was studied for the bromination of 1 (R = H) (Table II).

The situation may be expressed by the equations

$$Br_3^- \overset{K}{\rightleftharpoons} Br^- + Br_2$$

$$1 + Br_2 \overset{k_2}{\rightarrow} 7$$

$$1 + Br_3^- \overset{k_2'}{\rightarrow} 7$$

where $K = [Br_2][Br^-]/[Br_3^-]$. When bromide ion is present in excess, the observed second-order rate constant should have the form

$$k_2^{obsd} = \frac{k_2K + k_2'[Br^-]}{K + [Br^-]} \quad (1)$$

However, if reaction via tribromide ion is negligible ($k_2' \simeq 0$) eq 1 reduces to

$$k_2^{obsd} = k_2K/(K + [Br^-]) \quad (2)$$

and thus k_2^{obsd} should diminish as the concentration of bromide ion is increased. This trend is evident in the observed data shown in Table II which is best analyzed in terms of the reciprocal form of eq 2

$$\frac{1}{k_2^{obsd}} = \frac{1}{k_2} + \frac{[Br^-]}{k_2K} \quad (3)$$

As shown in Figure 2 a plot of $1/k_2^{obsd}$ vs. $[Br^-]$ yields an excellent straight line[19] from whose slope and intercept[19] we calculate $k_2 = 30.3\ M^{-1}\ min^{-1}$ and $K = 0.0554$ M. This value of K, which applies to 30 °C, is very close to that obtained by Bell[20] (0.0562) for 25 °C. If reaction via tribromide ion were appreciable (>1%) the plot in Figure 2 would show significant curvature at the higher bromide ion concentrations.

Table II. Variation of the Rate of Bromination of 4(3*H*)-Quinazolinone (1, R = H) with $[Br^-]$[a]

$[Br^-]$, M	k_2^{obsd}, M^{-1} min^{-1}	$1/k_2^{obsd}$, M min	$k_2^{obsd}(K + [Br^-])$,[b] min^{-1}
0.01	25.7	0.0389	1.68
0.02	22.1	0.0453	1.67
0.03	19.6	0.0510	1.67
0.05	16.0	0.0625	1.69
0.10	10.8	0.0926	1.68
0.15	8.16	0.1226	1.68

[a] At 30 °C, [1] = 5.0×10^{-3} M, acetate buffer pH 3.55. Each k_2^{obsd} is the average of two determinations differing by 2% or less. Reciprocal data plotted in Figure 2. [b] Uses $K = 0.0554$ M derived from Figure 2.

Table III. Variation of Rates of Bromination of 1 (R = H), 1 (R = Me), and 2 (R = R' = Me) Perchlorate with pH[a]

Substrate	pH	k_2^{obsd}, M^{-1} min^{-1}	Log k_2^{obsd}	No. of runs
1 (R = H)	0.29	0.333	−0.476	3
	0.59	0.685	−0.164	3
	0.98	1.55	0.190	3
	1.27	2.39	0.378	3
	1.66	6.49	0.812	2
	1.94	9.32	0.969	3
	2.23	15.9	1.20	2
	2.63	21.1	1.32	3
	2.80	21.2	1.33	2
	3.07	25.4	1.40	2
	3.55	25.7	1.41	2
	3.97	25.9	1.41	2
1 (R = Me)	0.30	0.512	−0.291	2
	0.60	0.945	−0.025	2
	0.99	2.32	0.365	2
	1.27	4.39	0.642	2
	1.60	8.38	0.923	2
	1.78	12.7	1.10	2
	2.24	19.3	1.29	2
	2.40	25.6	1.41	2
	2.82	30.3	1.48	2
	3.14	36.3	1.56	2
	3.38	41.1	1.61	2
	3.61	40.0	1.61	2
2 (R = R' = Me)	0.29	1.56	0.193	4
	0.58	3.53	0.548	4
ClO_4^-	0.96	7.41	0.870	2
	1.23	15.1	1.18	2
	1.50	28.5[b]	1.46	2
	1.84	68.1[b]	1.83	4

[a] At 30 °C, [substrate] = 5.0×10^{-3} M, $[Br_2] \simeq 5.0 \times 10^{-4}$ M, [KBr] = 0.01 M. For pH 0 → 2 dilute sulfuric acid, pH 2 → 3 chloroacetate buffers, pH 3 → 4 acetate buffers. The values of k_2^{obsd} are the average of two or more determinations as indicated in column 5. [b] [Substrate] = 2.5×10^{-3} M, $[Br_2] \simeq 3.0 \times 10^{-4}$ M.

As a further check on the unimportance of reaction via tribromide ion we note that eq 2 requires that the term $k_2^{obsd}(K + [Br^-])$ remain constant over a range of bromide ion concentration. Column 4 of Table II shows that for the present data this term does indeed remain constant. If tribromide ion had $k_2' = 0.3\ M^{-1}\ min^{-1}$ (i.e., 1% of k_2) the term would rise from 1.68 to 1.72 over the range of bromide ion concentration studied.

In summary, we conclude that bromination by tribromide ion is negligible (<1%) with respect to reaction via molecular bromine.

Acidity Dependence. The rates of bromination of 1 (R

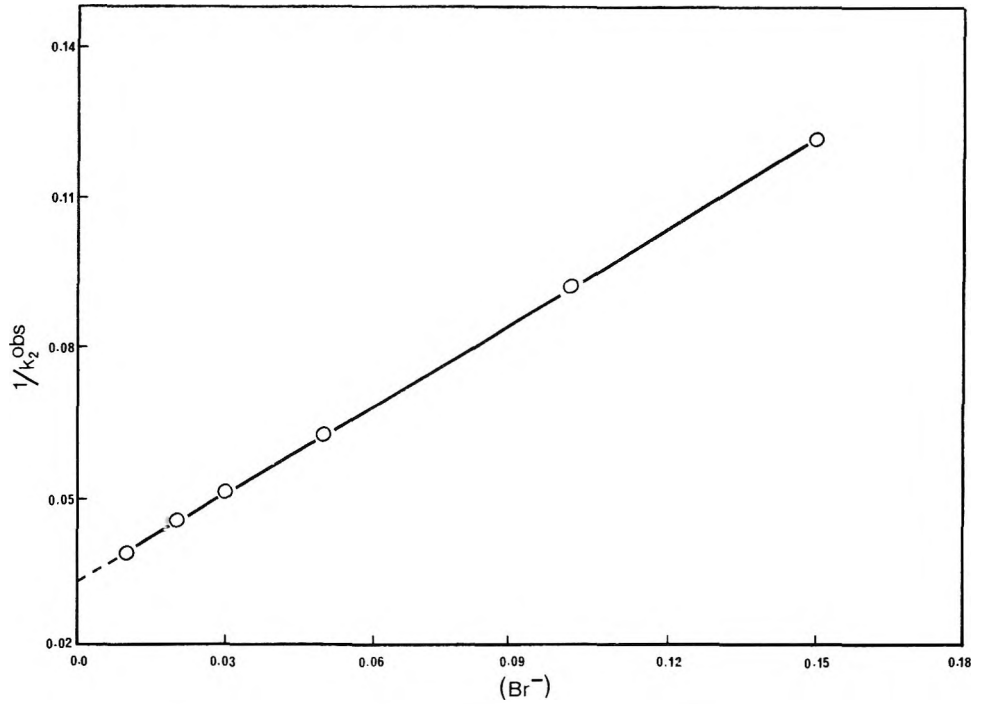


Figure 2. Variation of the rate of bromination of 4(3*H*)-quinazolinone (1, R = H) with [Br^-].

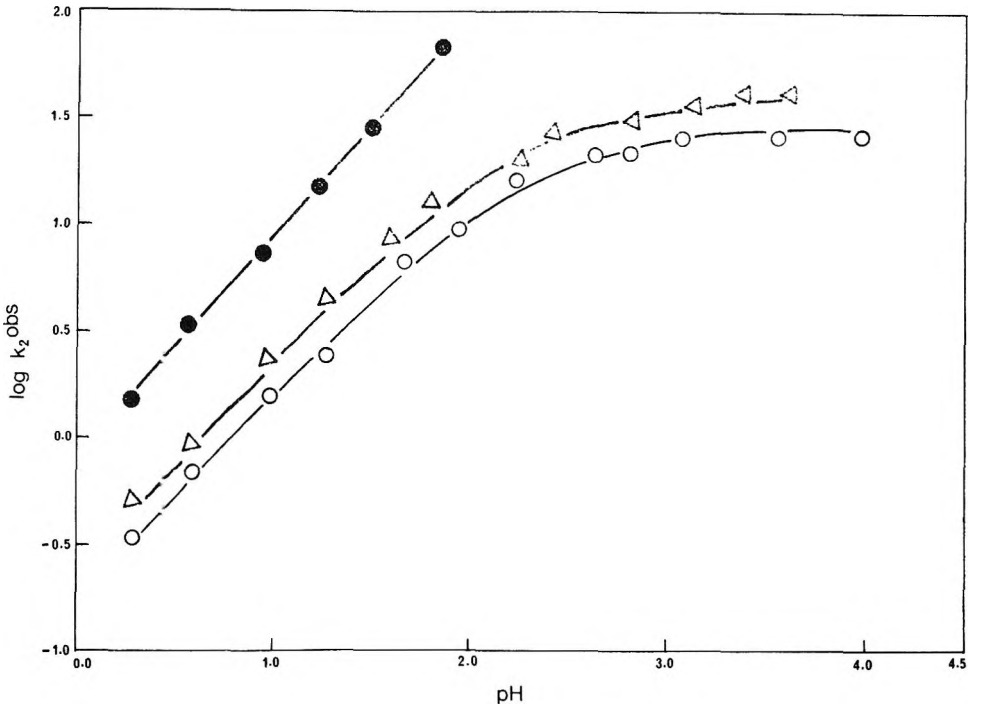


Figure 3. Acidity dependence of the rates of bromination of the substrates: ○, 1 (R = H); △, 1 (R = Me); ●, 2 (R = R′ = Me) perchlorate.

= H), 1 (R = Me), and 2 (R = R′ = Me) perchlorate were measured at various acidities in dilute sulfuric acid and in buffer solutions.[21] The data obtained are given in Table III and are plotted in Figure 3.

The rate data for the 1,3-dimethyl cation (2, R = R′ = Me) increase linearly[22] with pH in the manner appropriate for the reaction taking place upon the pseudobase 3 (R = R′ = Me). As described in the Experimental Section this pseudobase may be observed, and the pK for its formation is about 7.

The rate profiles for the parent 1 (R = H) and the 3-methyl derivative 1 (R = Me) are consistent with reaction taking place upon their free base forms, since the known[23,24] pK_a's for their conjugate acids 2 (R = H, Me; R′ = H) are 2.12 and 2.18 (at 20 °C), respectively. However, the rate profiles are also consistent with the reaction taking place upon species, such as the covalent hydrates 3 (R = H, Me; R′ = H), that are in equilibrium with the free bases 1 (R = H, Me) in a manner that is independent of acidity.[7a]

In the region pH <2 where all three substrates exist predominantly as cations they react with bromine at very similar rates. For example at pH 0.29 the relative rates of 1 (R = H) to 1 (R = Me) to 2 (R = R′ = Me) are 1.00:1.54:4.68. These similarities are strongly suggestive that the three substrates react via very similar mechanisms, with the small rate differences being attributable to the normal acti-

Table IV. Uv Spectral Data and Ionization Constants of the Substrates and Their Bromination Products

Compd	pK_a	pH	λ_{max}, nm (log ϵ)	Ref
1 (R = H)		2.23	255 (3.76), 261 (3.77), 283 (3.68), 291 (3.65)	This work
	2.12	7.00	226 (4.42), 231 (4.39), 263 (3.75), 269 (3.71), 292 (3.46), 311 (3.61), 313 (3.54)	23, 44
1 (R = Me)	2.18	1.0	229 (4.34), 234 (4.39), 279 (3.78), 293 (3.74), 303 (3.59)	24
		7.0	225 (4.42), 266 (3.80), 272 (3.78), 290 (3.43), 301 (3.56), 313 (3.49)	44
2 (R = R′ = Me), ClO_4^-		2.10	273 (3.77), 283 (3.77), 294 (3.67)	This work
7 (R = H)		0.29	266 (3.97), 293 (3.72), 302 (3.56)	This work
7 (R = Me)		2.10	264 (3.85), 297.5 (3.37), 311.3 (2.23)	This work
6 (R = R′ = Me), ClO_4^-		2.10	274 (3.96), 294 (3.80), 305 (3.66)	This work

vating effect on methyl groups upon electrophilic substitution. Since the cation **2** (R = R′ = Me) almost certainly reacts via its pseudobase **3** (R = R′ = Me), this requires that 4(3*H*)-quinazolinone (**1**, R = H) and its 3-methyl derivative **1** (R = Me) react via their covalent hydrates **3** (R = H, Me; R′ = H).

The mechanism proposed, then, is that shown in Scheme I. In this, the covalent hydrates (or pseudobase) **3**, in equilibrium with the cations **2**, react with molecular bromine to give intermediates **4** in the rate-determining step.[25] Proton loss[25] from **4** gives the covalent hydrates (or pseudobase) **5** in equilibrium with the product cations **6**.

The kinetically significant steps of the mechanism are

$$1 + H^+ \overset{K_a}{\rightleftharpoons} 2 \overset{K}{\rightleftharpoons} H^+ + 3 \overset{k_2,\ Br_2}{\longrightarrow} \text{products}$$

For this sequence

$$\text{rate} = k_2^{obsd}[2]_S[Br_2] = k_2[3][Br_2] \quad (4)$$

where $[2]_S$ is the stoichiometric concentration of the cation ($[1] + [2] + [3]$). If we define $K_a = [1][H^+]/[2]$ and $K = [3][H^+]/[2]$ then it follows from eq 4 that

$$k_2^{obsd} = \frac{k_2K}{(K_a + [H^+] + K)} \quad (5)$$

In the region of acidity studied, the observed data (Table III, Figure 3) are completely in accord with this equation.

For the dimethyl cation **2** (R = R′ = Me) the equilibrium $1 \rightleftharpoons 2$ does not exist and so the term K_a disappears from eq 5. Moreover, the equilibrium constant $K \simeq 10^{-7} \ll [H^+]$ at the acidities used, and so eq 5 simplifies to

$$k_2^{obsd} = k_2K/[H^+] \quad (6)$$

This equation requires that a plot of log k_2^{obsd} vs. pH should give a straight line of unit slope. The least-squares line[22] through the data in Figure 3 has a slope of 1.04.

For the substrates **1** (R = H, Me) the constant $K_a \simeq 10^{-2}$, whereas K is probably 10^{-5}–10^{-6} [since for the dimethyl cation **2** (R = R′ = Me) $K \simeq 10^{-7}$], and so eq 5 may be reduced to

$$k_2^{obsd} = k_2K/(K_a + [H^+]) \quad (7)$$

The logarithmic form of this equation

$$\log k_2^{obsd} = \log k_2K - \log (K_a + [H^+])$$

generates curves such as those shown by the observed data in Figure 3. The curve drawn through experimental points for **1** (R = H) was calculated from eq 7 using[27] $k_2K = 0.171$ min^{-1}, and $K_a = 10^{-2.21}$. The agreement between the calculated curve and the experimental points is excellent. Similarly, the curve drawn for **1** (R = Me) using[27] $k_2K = 0.256$ min^{-1} and $K_a = 10^{-2.21}$ gives an excellent fit to the observed data. The slight differences between the pK_a's used here (2.21, 2.21) and those determined experimentally (2.12, 2.18)[23,24] are probably not significant, although, of course, the former apply to 30 °C, whereas the latter apply to 20 °C.

The observed kinetic data, then, are entirely consistent with the mechanism proposed in Scheme I in which the substrates **1** (or **2**) react with bromine via their covalent hydrates (or pseudobase) **3**. Similar conclusions were arrived at earlier for the hydrogen–deuterium exchanges and brominations of 2(1*H*)-pyrimidinones[7] and 4(3*H*)-pyrimidinones.[8]

Relative Reactivities. As a final point we look at the relative reactivities of the three substrates in terms of the proposed mechanism. The numerator term k_2K of eq 6 and 7 is not separable except for the dimethyl cation **2** (R = R′ = Me). However, this composite term may be obtained[27,28] and compared for the three cations **2**.

Cation **2**	R = R′ = H	R = Me; R′ = H	R = R′ = Me
k_2K, min^{-1}	0.171	0.256	0.800
Rel	1.00	1.50	4.68

The introduction of R = Me at N_3 causes only a slight increase in rate. It should decrease the equilibrium constant K, and so there must be a compensating increase in k_2. A more substantial increase in rate is caused by the introduction of R′ = Me at N_1. Again its effect should be to decrease K, but clearly this is overshadowed by a larger increase in k_2 due to the ability of the methyl group at N_1 to help stabilize the cationic intermediate **4** (R = R′ = Me).

For the dimethyl cation **2** (R = R′ = Me) $K \simeq 10^{-7}$, and so $k_2 = 0.8 \times 10^7$ M^{-1} min^{-1} (4.6×10^5 M^{-1} sec^{-1}).[29] This value is quite reasonable since second-order rate constants for the attack of bromine upon simple alkyl anilines fall in the range 10^6–10^{10} M^{-1} sec^{-1}.[18,20]

In summary, both the relative reactivities and the absolute reactivities of the three substrates are compatible with the proposed mechanism.

Experimental Section

The melting points given below are uncorrected. Uv measurements were made on a Cary 14 instrument, ^{1}H NMR spectra were obtained from a Varian A-60 spectrometer, and ir spectra were run on a Perkin-Elmer 425 spectrophotometer as KBr disks. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Ultraviolet spectral data for the substrates and their 6-bromo derivatives are presented in Table IV.

4(3*H*)-Quinazoline (1, R = H), which was prepared by the reaction of anthranilic acid and formamide,[30] was methylated to produce **3-methyl-4-quinazolinone (1, R = Me).**[10]

6-Bromo-4(3*H*)-quinazolinone (7, R = H) was prepared by cyclization,[11] and by direct bromination.

1 (R = H) (1.46 g, 0.01 mol) was stirred overnight in 30 ml of water containing bromine (1.6 g, 0.01 mol) and KBr (1.19 g, 0.01 mol). The resulting orange-white slurry was warmed until the orange color due to bromine disappeared, cooled, filtered off, washed with a little acetone, and dried at 75 °C. Recrystallization from methanol–DMF gave fine white crystals (2.1 g, 94%), mp 260–264 °C (lit.[11] 261–273 °C). The ir spectrum was identical with that of material made from the cyclization[11] of 5-bromoanthranilic acid.

5-Bromoanthranilic acid was prepared by a modification of the method of Wheeler and Oates.[32]

Anthranilic acid (13.7 g, 0.1 mol) in 120 ml of glacial acetic acid was stirred until all the solid dissolved (0.5 h). Bromine (16.0 g, 0.1 mol) in 50 ml of acetic acid was added dropwise over a period of 1.25 h. The resulting light yellow slurry was filtered off and washed with water and then with benzene. Recrystallization from 95% ethanol gave 15.4 g (71.4%) of the desired compound, mp 210–213 °C (lit.[32] 213 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 39347).

6,8-Dibromo-4(3*H*)-quinazolinone (9). 3,5-Dibromoanthranilic acid (14.7 g, 0.05 mol) and formamide (6.75 g, 0.15 mol) were heated together at 210 °C for 30 min. After cooling the crystalline slurry was filtered off, washed with water and then with ethanol, and recrystallized from methanol–DMF to give 16.0 g (86.3%) of **9**, mp 340 °C dec (lit.[32] 337 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 45518).

3,5-Dibromoanthranilic acid required for the above was prepared as follows.

A solution of bromine (32 g, 0.2 mol) in 50 ml of glacial acetic acid was added dropwise to anthranilic acid (13.7 g, 0.1 mol) in 200 ml of the same solvent. The resultant slurry was stirred for 40 h, and then heated on a water bath for 2 h. The yellow precipitate was filtered off, washed with benzene, and dried at 75 °C. Recrystallization from 90% aqueous ethanol gave 21.9 g (74.9%) of product, mp 229–231 °C (lit.[32] 230–232 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 43810).

6-Bromo-3-methyl-4-quinazolinone (7, R = Me) (as HBr salt). Bromine (0.8 g, 5 mmol) in 10 ml of 80% aqueous methanol was added to 1 (R = Me) (0.8 g, 5 mmol) in 10 ml of the same solvent. The yellow solution was stirred for 5 h at room temperature and then the white precipitate was filtered off and washed with water. Recrystallization from 95% aqueous ethanol gave 1.1 g (68.8%) of **6** (R = Me; R′ = H) bromide: mp 338–340 °C; ir (KBr) 1700 (C=O), 1610 (C=N), 1360 cm^{-1} (N–Me); uv, see Table IV; ^1H NMR (Me_2SO-d_6, Me_4Si) δ 3.52 (s, N_3CH_3), 7.63–8.35 (m, aromatic), 8.63 (s, C_2H).

Anal. Calcd for $C_9H_8N_2OBr_2$: C, 33.78; H, 2.52; N, 8.75. Found: C, 33.79; H, 2.67; N, 8.76.

Attempts to prepare this compound (**7**, R = Me) by methylation or by cyclization failure, but it was successfully converted to **6** (R = R′ = Me) iodide and thence to **6** (R = R′ = Me) perchlorate which was identical with the material obtained by direction bromination of **2** (R = R′ = Me) perchlorate.

1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium (2, R = R′ = Me) iodide was prepared by the method of Bogert and Geiger.[33] The corresponding **2** (R = R′ = Me) perchlorate[34] was prepared as follows.

A solution of silver perchlorate (4.15 g, 0.02 mol) in 10 ml of methanol was added to 2 (R = R′ = Me) iodide (6.04 g, 0.02 mol) in 200 ml of warm methanol, and was stirred at 40 °C for 0.5 h. The mixture was cooled, the silver iodide was filtered off, and the filtrate was evaporated. Recrystallization of the residue from ethanol–water gave 4.67 g (85%) of 2 (R = R′ = Me) perchlorate: mp 254–257 °C; ir (KBr) 1715 (C=O), 1654 (C=N), 1386 (N–Me), 1110–1060 cm^{-1} (ClO_4^-); uv in Table IV.

Anal. Calcd for $C_{10}H_{11}N_2O_5Cl$: C, 43.73; H, 4.04; N, 10.20. Found: C, 43.90; H, 3.91; N, 10.20.

6-Bromo-1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium (6, R = R′ = Me) Iodide. Methyl iodide (1.0 g, 7 mmol) and **7** (R = Me) (1.2 g, 5 mmol) were heated together at 120 °C in a sealed tube for 12 h. The crystalline mass was washed with methanol and recrystallized from ethanol–water to give 1.64 g (86%) of the desired compound: mp 287–288 °C; ir (KBr) 1700 (C=O), 1645 (C=N), 1375 cm^{-1} (N–Me); ^1H NMR (Me_2SO-d_6, Me_4Si) δ 3.66 (s, N_3CH_3), 4.08 (s, N_1CH_3), 7.96–8.49 (m, aromatic), 9.99 (s, C_2H).

Anal. Calcd for $C_{10}H_{10}N_2OBrI$: C, 31.52; H, 2.65; N, 7.35. Found: C, 31.58; H, 2.62; N, 7.32.

The corresponding **6** (R = R′ = Me) perchlorate[34] was made in two ways.

A. From the Iodide. Silver perchlorate (0.207 g, 1 mmol) in 10 ml of ethanol was added to the above **6** (R = R′ = Me) iodide (0.381 g, 1 mmol) in hot aqueous ethanol, and the silver iodide precipitate was filtered off. Cooling the filtrate gave crystals of the perchlorate, which were recrystallized from aqueous ethanol to yield 0.332 g (94%) of **6** (R = R′ = Me) perchlorate: mp 395–397 °C; ir (KBr) 1708 (C=O), 1650 (C=N), 1381 (N–Me), 1100–1050 cm^{-1} (ClO_4^-); uv in Table IV; ^1H NMR identical with that of the iodide.

Anal. Calcd for $C_{10}H_{10}N_2O_5BrCl$: C, 33.97; H, 2.85; N, 7.92. Found: C, 34.23; H, 2.71; N, 7.94.

B. By Bromination. Bromine (0.8 g, 5 mmol) in methanol was added to **2** (R = R′ = Me) perchlorate (1.37 g, 5 mmol) dissolved in warm 80% aqueous methanol. The mixture was stirred for 2 h until the yellow color disappeared. The crystalline precipitate was filtered off, washed with methanol, and recrystallized from 80% aqueous ethanol to give 1.62 g (91.5%) of **6** (R = R′ = Me) perchlorate, mp 394–397 °C, spectral properties as in A above.

o-(Methylamino)-*N*-methylbenzamide (10) was made by two different routes which gave identical materials, even though our melting points differ considerably from those in the literature.

A. From 2 (R = R′ = Me) Iodide.[35,36] Twenty milliliters of 2 N NaOH solution was added to 2 (R = R′ = Me) iodide (1.51 g, 5 mmol) in 20 ml of water, and the mixture was stirred at 40 °C for 1 h. After cooling, the white slurry precipitate was filtered off, washed with water, and recrystallized from cyclohexane to give 0.80 g (98%) of **10**: mp 83–85 °C (lit.[36,37] 43–45, 70–72 °C); ir (KBr) 3280 (amide NH), 2870 (N–Me), 2800 (N–Me), 1610 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6, Me_4Si) δ 2.87 (s, –NHMe), 2.78 (s, –CONHMe), 7.60 (–NHMe), 6.17 (s, –CONHMe), 6.27–7.32 (m, aromatic).

B. From *N*-Methylisatoic Anhydride.[37] To *N*-methylisatoic anhydride (11.7 g, 0.066 mol) in 30 ml of water was added 15 ml of 30% aqueous methylamine, and the mixture was stirred and heated for 30 min. The clear top layer was decanted off, and upon cooling it gave white needles which were filtered off and recrystallized from cyclohexane to give 10.25 g (95%) of **10**, mp 84–86 °C (lit.[37] (43–45 °C), spectral properties identical with those given in A above.

Kinetic Procedures. All inorganic reagents were of analytical grade. Sulfuric acid, sodium thiosulfate, and starch solutions were prepared from commercial standard volumetric concentrates. Buffer solutions (0.2 M) were prepared after Vogel[38] and Perrin.[39] The acidities of all substrate solutions were measured using a Beckman Expandomatic pH meter. The pH values thus obtained for sulfuric acid solutions were, within experimental error, the same as those calculated[40] on the basis of the known pK_a's of 1 (R = H) and 1 (R = Me) where applicable.

Initial experiments suggested a second-order reaction between the substrates and bromine, and so subsequently all kinetic runs were carried out under pseudo-first-order conditions with an approximate tenfold excess of substrate. The reaction was most conveniently[40] followed by monitoring the disappearance of bromine titrimetrically as follows.

A stock solution containing potassium bromide (0.01 M) in the desired acid or buffer solution made up. Using this medium separate 50-ml solutions of bromine ($1.0–1.6 \times 10^{-3}$ M) and of substrate (1.0×10^{-2} M) were then prepared. The pH of the substrate solution was recorded. The flasks containing the bromine and the substrate solutions were wrapped in foil to prevent deterioration due to light, and were then equilibrated in a constant-temperature bath at 30.0 ± 0.2 °C for at least 15 min. At the start of a timer the substrate solution was added to the bromine solution, and the mixture was thoroughly shaken[41] and returned to the bath.

At appropriate time intervals 5-ml aliquots of the reaction mixture were withdrawn and quenched in 20 ml of 5% potassium iodide solution. The liberated iodine was titrated immediately against a standard 0.01 M sodium thiosulfate solution contained in a Metrohm E274 semiautomatic microburet (5-ml capacity, graduated in 0.005 ml) using 1% starch indicator.

Depending upon the rate of the reaction between 7 and 17 aliquots were drawn over a period extending well beyond 1 half-life. For the fast runs, the aliquots were quenched in the potassium iodide solution, and stored in the dark until time permitted their titration in rapid succession.

From the titration data $[Br_2]$ was calculated for various times t, and linear least-squares analysis in terms of the equation $\ln [Br_2] = \ln [Br_2]_0 - k_1 t$ was used to obtain a pseudo-first-order rate constant k_1. All kinetic runs were carried out at least twice, and only those were accepted which gave correlation coefficients >0.9998 in the least-squares analysis.

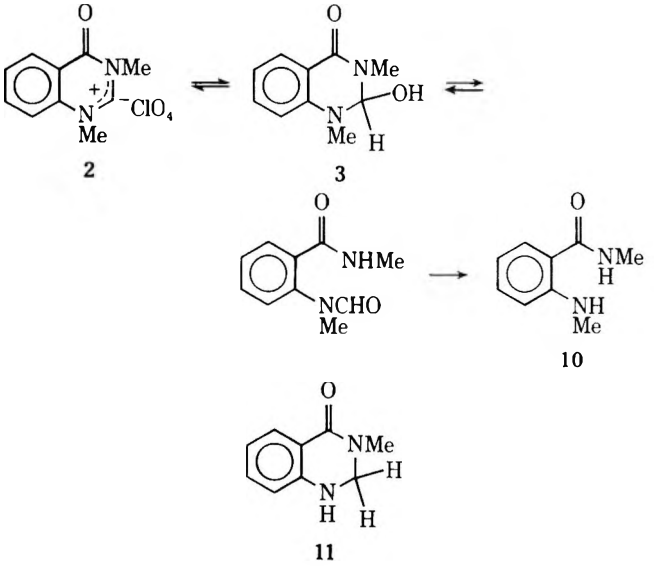
Strictly speaking the second-order rate constant k_2 should be

obtainable from the pseudo-first-order rate constant by $k_2 = k_1/[S]$. However, following Bell,[20] we used $k_2 = k_1/([S] - [Br_2]_0)$ to give a better estimate of k_2, since the excess of substrate over bromine is not particularly large.

The best curves to fit the data for **1** (R = H or Me) in Figure 3 were obtained by an iterative technique. Equation 7 requires that the term $k_2^{obsd}(K_a + [H^+]) = k_2K$ = a constant. A computer program was written which, given a value of pK_a, calculates values of this constant for the observed data set of k_2^{obsd} and pH, and then computes the average value of this constant. Using this averaged value of k_2K in eq 7 the program then calculates a value of k_2^{obsd} (k_2^{calcd}, say) for each pH and the standard deviation of log k_2^{obsd} with respect to log k_2^{calcd}. This process is repeated for various values of pK_a, and the best value is chosen such that the standard deviation of log k_2^{obsd} from log k_2^{calcd} is a minimum. In the present instances this also coincides with the lowest standard deviation of $k_2^{obsd}(K_a + [H^+])$ values from their average.

Pseudobase Formation. Since it is postulated that bromination of the cation **2** (R = R′ = Me) proceeds via the pseudobase **3** (R = R′ = Me), attempts were made to observe the equilibrium between these two species.

The solubility of **2** (R = R′ = Me) perchlorate in D_2O is too low to obtain decent NMR spectra. The salt can be dissolved in dilute NaOD solution, but in this medium it underwent ring opening and irreversible hydrolysis to *o*-(methylamino)-*N*-methylbenzamide (**10**) (cf. ref 35, 37).



Pseudobase formation was observed, however, by uv spectroscopy. The uv spectrum of **2** (R = R′ = Me) perchlorate in water (1.0×10^{-3} M) was recorded. Upon addition of some dilute NaOH solution, a new band at 330 nm appeared. When an equivalent amount of dilute HCl was added, this band disappeared, and the original spectrum was retraced. Since the uv spectrum of 2,3-dihydro-3-methyl-4-quinazolinone (**11**)[42] in MeOH has a band at 338 nm, the 330-nm band is ascribed to the pseudobase **3** (R = R′ = Me). Note, however, that addition of an excess of dilute NaOH solution again resulted in irreversible formation of **10**.

Potentiometric titration[43] of the salt **2** (R = R′ = Me) perchlorate with dilute NaOH solution suggested that the equilibrium constant $K = [3][H^+]/[2] \simeq 10^{-7}$. Three separate titrations gave values of $pK \simeq 7.1, 7.2, 7.5$. Back titration with acid *did not* give pH values corresponding to these values, but rather to a pK value about 3.5. In a separate experiment the protonation pK value of **10** was determined spectrophotometrically[43] to be 3.77. During the titration experiments on **2** (R = R′ = Me) perchlorate the pH values after the addition of several aliquots of base were not steady. Immediately following a further addition, the pH rose as expected, but subsequently peaked and then fell. It appears, therefore, that during the latter parts of the titrations there was significant irreversible opening of the pseudobase **3** (R = R′ = Me) to **10**.

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Registry No.—**1** (R = H), 491-36-1; **1** (R = Me), 2436-66-0; **2** (R = R′ = Me) perchlorate, 57573-55-4; **2** (R = R′ = Me) iodide, 2453-94-3; **6** (R = R′ = Me) perchlorate, 57573-56-5; **6** (R = R′ = Me) iodide, 57573-58-7; **7** (R = H), 32084-59-6; **7** (R = Me), 57573-59-8; **7** (R = Me) HBR, 57573-60-1; **10**, 32212-33-2; *N*-methylisatoic anhydride, 10328-92-4.

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(13) Least-squares slope 23.07 M^{-1} min^{-1} (SD 0.58), intercept 0.20 min^{-1} (SD 0.83), correlation coefficient 0.9994.
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(17) $[HOBr][H^+][Br^-]/[Br_2] = 9.6 \times 10^{-9}$ M^2 (25 °C). J. M. Pink, *Can. J. Chem.*, **48**, 1169 (1970).
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(19) Least-squares slope 0.5961 (SD 1.98×10^{-3}), intercept 3.304×10^{-2} (SD 9.81×10^{-5}), correlation coefficient 0.999978.
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(21) In acetate buffers of pH >4 the rate of bromination of **1** (R = H) decreases owing to the onset of significant (>1%) formation of HOBr,[17] and also owing to a process involving acetate ion. This was shown by carrying out kinetic runs at fixed pH (5.32), but with varying buffer concentration. With increasing acetate concentration (0.085, 0.128, 0.17 M) the rate constant (k_2^{obsd}) diminished (12.5, 8.25, 5.76 M^{-1} min^{-1}). The formation of acetyl hypobromite from $AcO^- + Br_2 \rightleftarrows AcOBr + Br^-$ would require a linear relationship between $1/k_2^{obsd}$ and $[AcO^-]$, whereas the data more closely fit a relationship between $1/k_2^{obsd}$ and $[AcO^-]$ *squared*. A similar, but numerically different, reduction in rate was obtained for a bromination in a phosphate buffer. Again the reduction is not solely attributable to HOBr formation.
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(27) The values of k_2K and K_a were arrived at as described in the Experimental Section.
(28) The k_2K term for the dimethyl cation is derived from the intercept (log k_2K) of the straight line[22] in Figure 3.
(29) If we take into account the reduction (15.3%) in free bromine concentration due to tribromide formation, this value is raised to 1.5×10^5 M^{-1} s^{-1}.
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Electrochemistry of Natural Products. IV. Electrochemical and Chemical Oxidative Dimerization of 1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline[1]

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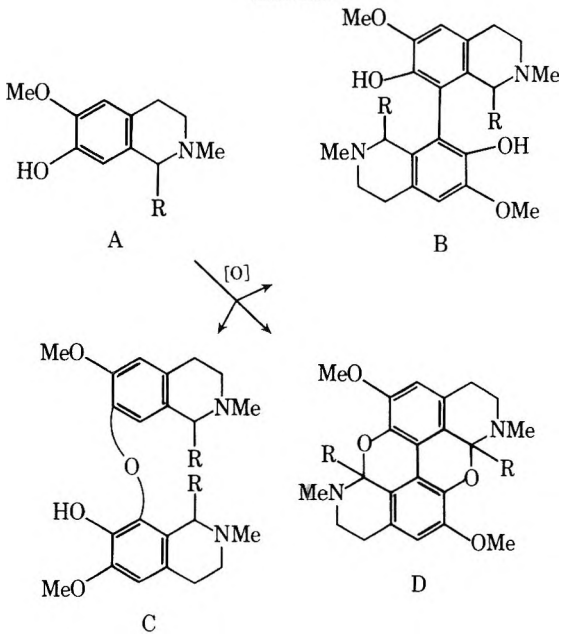
Racemic 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**1**) has been oxidatively coupled by controlled-potential electrolysis in excess base to yield one (**3**) of three possible isomers of the carbon–carbon dimer. The reaction was carried out at +0.16 V (vs. SCE) in wet acetonitrile at a graphite felt anode with tetraethylammonium perchlorate as an electrolyte. Other reaction conditions gave the same stereochemical results in poor yields. During the oxidation, only molecules of **1** having the same configuration at C-1 coupled with each other to form product (*R* with *R* and *S* with *S*). Furthermore, only one of two possible rotational isomers was formed. The structure of the single product was established by the chemical [$K_3Fe(CN)_6$] and electrochemical oxidation of racemic **1** and its enantiomers. Additional products of the chemical oxidation are described.

In a previous paper of this series,[2] we studied the electrochemical and catalytic oxygenation of 1-alkyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (A) and established the general structures of the products as B, C, and D (Scheme I). All three products were formed as

Scheme I



mixtures of stereoisomers, but only B could be resolved into its components. The centers of chirality at C-1 of B (when R = CH_3) and the newly formed center caused by restricted biphenyl rotation lead to the possible formation of three sets of enantiomers: **2**, **3**, and **4**, designated as *RS*, *SS* rotamer A, *SS* rotamer B, and their enantiomers, respectively (Scheme II). All three isomers of B (R = CH_3) were obtained from the catalytic oxygenation of A (R = CH_3) although specific stereochemical structures were not established. When the electrooxidation of **1** was carried out in acetonitrile solution,[3] only one of the three possible isomers of B was obtained. In this paper, we would like to describe the structure elucidation of the single stereochemical product and to discuss the implications of its formation.

Structures of the Three Carbon–Carbon Dimers 2, 3, and 4. Three dimers were isolated from the catalytic oxygenation of racemic **1** over a Pt catalyst: two crystalline compounds melting at 132–134 and 222–224° and one noncrystalline glass, all of which had characteristic spectral properties.[2] The general structures of the three dimers were confirmed in the present work by equilibrating them via oxygenation over platinum on carbon[2] of **3** to give a mixture of bis-3,4-dihydroisoquinolinium salts[5a] (the open form of a type D compound). The mixture was reduced with $NaBH_4$ to give a mixture of compounds **2**, **3**, and **4**, shown by direct chromatographic comparison.

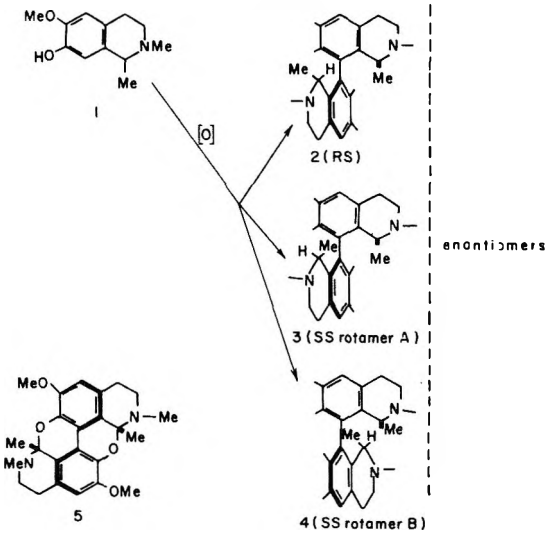
Electrooxidation of racemic **1** under a variety of conditions yielded only the isomer melting at 226–227°.[4] Of the three dimers, only **3** and **4** have the same configuration at C-1 of both isoquinoline rings. Since oxidation of the separated enantiomers of **1** (both *R* and *S*) yielded the enantiomers of the same products as obtained from racemic **1**, the single electrochemical product must be **3** or **4**, and must result from the coupling of identical stereoisomers of **1**. Oxidation of the separated enantiomers of **1** with $K_3Fe(CN)_6$ (which is not stereospecific)[5] yielded the appropriate enantiomers of **3** and **4** having the melting points of the two crystalline isomers (132–134[6] and 224–226°). Since both of these products must have identical configurations in the isoquinoline rings, the third noncrystalline dimer from the catalytic oxygenation of racemic **1** must have structure **2**. When the NMR spectra of the two crystalline dimers were measured in deuterated dimethyl sulfoxide, the C–CH_3 protons appeared at δ 0.71 for the compound melting at 226–227° and at δ 1.17 for the one melting at 132–134° (as compared with δ 1.22 in **1**). Molecular models of the two possibilities show that the CH_3 in **3** is located on top of the benzene ring whether the methyl group is axial or equatorial. In **4**, the methyl group is well away from the benzene ring when in the axial position but fairly close to it when

Table I. Oxidation of Racemic 1 and Its Enantiomers

Substrate, method	Products % yield (% conversion[a]) 2	3	4	C, R = CH_3	D, R = CH_3	C–C/ C–O–C[b]	Potential, V vs. SCE
rac-1							
$K_3Fe(CN)_6$[c] in NH_4OAc	11.4	8.3	4	2.8	1.8	8.5	
Electrolytic							
Excess NaOMe							
1 compartment		40.8 (44.4)		24.3 (26.5)		1.7	+0.16
2 compartment		68.9 (76.9)		6.8 (7.7)		10	+0.04
Sodium salt							
1 compartment		31.9 (32.9)		16.8 (17.8)		1.8	+0.01
2 compartment		41.1 (44.6)		22.2 (24.1)		1.8	+0.01
Neutral							
1 compartment		18.5 (24.7)		22.9 (30.4)		0.8	+0.22
2 compartment		47.0 (58.0)		14.8 (18.3)		3.1	+0.24–0.36
Hydrochloride							
1 compartment		10.1 (17.9)		13.8 (24.0)		0.7	+0.8
2 compartment		13.8 (17.4)		8.7 (11.6)		1.6	+0.6–0.8
Excess HCl[d]							
1 compartment		8.4 (21.3)		15.3 (31.6)	8.7 (19.7)	0.5	+1.16
2 compartment		11.1 (18.1)		8.0 (13.9)		1.4	+0.68
(*R*)-(+)-1							
$K_3Fe(CN)_6$ in NH_4OAc		17.4 (18.3)	20.9 (22.2)	4.4 (4.7)	1.7 (1.8)	8.6	
Electrolytic							
Excess NaOMe in two compartments		65.5 (87.3)		6.2 (8.3)		10	+0.16
(*S*)-(−)-1							
$K_3Fe(CN)_6$ in NH_4OAc		25.9 (27.8)	23.5 (25.5)	6.1 (6.6)	2.3 (2.7)	8.0	
Electrolytic							
Excess NaOMe in two compartments		62.2 (71.8)		5.5 (6.3)		10	+0.16

[a] Corrected for recovered starting material. [b] This ratio is the sum of the conversion yields of 2, 3, and 4 divided by C, R = CH_3. [c] Previous chemical oxidations of this compound are summarized in ref 5. [d] Oxidized in 0.1 N HCl.

Scheme II



equatorial. Since the NMR shift is very much like starting material for **4**, it seems reasonable to assign structure **4** to the low-melting isomer with the less shielded methyl group. It would also follow that the methyl group is more likely to be in a pseudoaxial position in both compounds, a good possibility in such a sterically hindered situation. Thus, the product of the electrochemical oxidation is **3**. The chiroptical properties of the enantiomers of both **3** and **4** have been studied[7] and found to be in general agreement with the assigned structures. It should be noted, however, that the assignments are based entirely on spectral properties and are not really definitive in a chemical sense.

Preparation and Resolution of 1. The racemic benzyl ether of **1** was prepared by a Bischler–Napieralski sequence as described by Strukov.[8] Treatment of this ether with di-*p*-toluoyl-*d*-tartaric acid and crystallization from ethanol yielded the less soluble salt of the *R* isomer. Similar treatment of the partially resolved bases recovered from the *d*-tartaric acid reaction with di-*p*-toluoyl-*l*-tartaric acid yielded the crystalline salt of the *S* base. The two salts had identical melting points and opposite rotations and were decomposed and debenzylated to yield the enantiomers of **1**. These enantiomers had identical properties and equal and opposite rotations and ORD curves. The absolute configuration of the enantiomers was established by methylation to yield carnegine (6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline) of known configuration.[9]

Potassium Ferricyanide Oxidation of 1 and Its Enantiomers. Racemic **1** was oxidized with $K_3Fe(CN)_6$ in an NH_4OAc system to yield the products shown in Table I. All three isomers of B (**2**, **3**, and **4**, R = CH_3) were separable and were characterized. Although C surely exists as a mixture of diastereomers, they could not be separated. A low yield of the polycyclic ether D (R = CH_3) was also obtained.[5] Corresponding oxidation of the enantiomers of **1** yielded the enantiomers of **3** and **4**, presumably one enantiomer of C (R = CH_3), and an optically active form of D (R = CH_3).[10]

Electrolytic Oxidation of 1 and Its Enantiomers. The oxidations were carried out under various conditions and yielded the products shown in Table I. Except for the acid oxidations, the solvent was wet acetonitrile and the electrolyte was tetraethylammonium perchlorate. Graphite felt anodes and platinum cathodes were used as previously described.[3] As portions of other work, the effect of platinum anodes[2,11a] and carbon paste anodes[11b,11c] in this reaction were studied. In both cases, very low yields of carbon–carbon dimer were isolated. Isomer **3** was the only carbon–carbon dimer isolated from *any* of the electrochemical reactions. The absence of isomers **2** and **4** was shown by direct comparison of the NMR spectra of the crude reaction mix-

tures with those of the pure isomers and by direct TLC comparison using wedge-shaped layers. Attempts were made to equilibrate the isomers **2**, **3**, and **4** at 30° in aqueous acetonitrile containing electrolyte and acid or base, but no change was observed. Only in the case of the acid oxidations was any of compound D (R = CH_3) obtained.

The enantiomers of **1** were oxidized under the optimum conditions (excess NaOMe) found for racemic **1** with the results shown in Table I.

Discussion

Three aspects of the data in Table I merit discussion: the stereoselectivity of the reaction; the variation of the ratio of carbon–carbon to carbon–oxygen–carbon dimers under various conditions; and the general mechanism of the electrolytic oxidation. The stereochemistry will be considered first since it may well underlie a discussion of the other aspects.

The stereochemical results of this work can best be explained as arising from a surface reaction, presumably at or near the electrode surface. While it seems logical to assume that electrochemical reactions are surface phenomena, this has not usually been thought to be the case. Most of the electrochemical reactions studied for stereochemical reasons have been reductions as recently summarized by Fry,[12] although oxidation has received attention from Eberson and Nyberg.[13] In all of this work as well as in recent experiments concerning asymmetric induction in electrochemical systems,[14] only a partial control has been attained, and there has been some controversy about whether electrochemical reactions involve surfaces at all.

It is generally accepted[15] that the electrode surface is covered with a more or less highly ordered system of solvent molecules and solvated electrolyte ions known as the *electric double layer* or more recently the *electrified interface*. This coating may extend into the solvent as much as 50 Å and is covered in turn with a second layer known as the *diffuse layer* which may extend another 100 Å.[13] Reactions can be visualized as taking place in the outer regions of these layers where the actual electrode surface would play a minimal role or in the inner region where the surface may play a major role. Thus, in order to observe surface phenomena similar to those found in catalytic hydrogenation, substrate molecules would have to show an attraction for the electrode surface sufficiently strong to penetrate the double layer before reaction. In the reactions described in this paper, the attraction between electrode and substrate should be quite strong, at least in base solutions. The working electrode, the anode in this case, is positively charged and the isoquinoline substrate (**1**) is an extremely electron-rich system with two oxygens (one an anion), an aromatic ring, and one nitrogen. Furthermore, the electron-rich centers or *binding sites* are spread over the whole molecule so that the molecule should be arranged in a plane parallel to the surface. This has, in fact, been shown for some of our isoquinoline molecules by Braun and Stock[16] using solid graphite electrodes and methylene blue as a standard. It has recently been shown that adsorption of aromatic rings to the anode plays a role in the product distribution from the Kolbe reaction,[17] and amine adsorption has been used extensively by Weinberg to explain reaction products.[18] Such an explanation is less valid in acid, but, as shown in Table I, the experimental conditions and results are also quite different in acid. Higher potentials must be used and the overall yields are relatively low. It should be noted that the best yields of carbon–carbon dimers are obtained in strong base where the phenol is present as an anion.

If one assumes a surface reaction of molecules in a near-

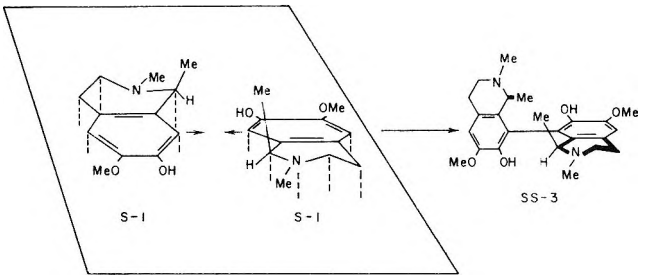
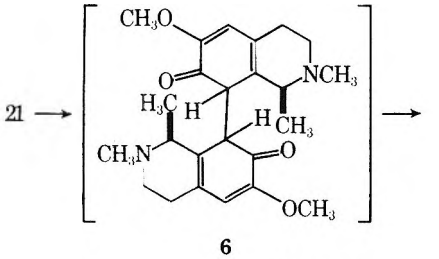


Figure 1. Oxidative coupling of (*S*)-**1** to *SS*-rotamer A, **3**.

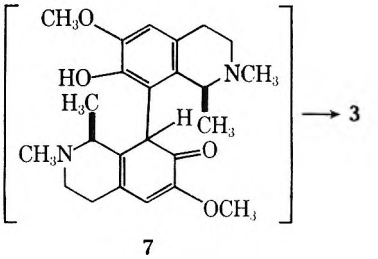
planar conformation, the electrolytic oxidation of **1** to **3** can be easily explained. Two facts must be accommodated: only molecules having the same configuration at C-1 can couple to form carbon–carbon dimers; and of the two possible configurations around the biphenyl bond (**3** and **4**), only one is formed. Reasoning from experience in catalytic hydrogenation, one would assume that the isoquinoline molecules would be adsorbed to the surface with the C-1 methyl group sticking up as shown in Figure 1. Under these conditions, only molecules having like configurations can come close enough together for carbon–carbon coupling to take place at C-8. When molecules having unlike configurations at C-1 are involved, a serious methyl–methyl interference prevents reaction. Thus, either **3** or **4** should result from the coupling of **1**.

The formation of **3** rather than **4** requires more subtle argument. On the basis of steric reasoning alone, one might expect **4** to be formed since the two methyl groups would then be pointed away from one another and would be in a separate quadrant of the molecule (assuming that the benzene rings are perpendicular to one another and that the molecule is bisected by two planes through them). In the actual product, **3**, the methyl groups face one another in the same quadrant. The formation of **3** can be explained superficially[1a] if one assumes that the isoquinoline rings are not completely parallel with the surface, but are tilted so that the more planar aromatic ring is closer to the surface than the aliphatic heterocyclic ring (Figure 1). If coupling takes place from these tilted conformations and rotation around the biphenyl bond is forbidden after coupling, **3** will be formed exclusively.

It has been pointed out by a reviewer, however, that such a superficial view may not be correct. The following rationale is a blend of his ideas and ours. The intermediate arising from the coupling of **1** will have either structure **6** or **7** depending upon whether the coupling is free radical (**6**) or ionic (**7**) (see below). If **6** is formed first, it must go by suc-



6



7

cessive deprotonation to **7** and to **3**. The exact nature of this deprotonation would determine the structure of **3**. Since the stereospecificity is lost when the oxidation is carried out in solution with ferricyanide (which should also proceed through intermediates **6** and **7**), it seems that the surface or its coatings must still play a role in the deprotonation. If the protons are removed from the intermediate from the surface side of the dimer while it is in place on the surface, or is just leaving, the product should be **3**, possibly owing to the superficial "tilting" argument given above. Since the electrode would be expected to contain base sites, either methoxide ions or water molecules, in its double layer (see above), such a deprotonation is quite plausible. This deprotonation by surface adsorbed base sites could then explain a stereospecific removal of protons and would be tantamount to arguing that deprotonation takes place from a least hindered side. If the "tilting" argument is rejected, it could be rationalized that the conformation of intermediate **7** is such as to produce **3** when the proton is least hindered and most subject to removal. From a study of the Dreiding models of **7**, this would be quite reasonable.

The question of whether carbon–carbon (B) or carbon–oxygen–carbon dimers (C) are formed has been quite important in natural systems[19] where both do occur, but generally not simultaneously. In chemical systems[5c] attempts have been made, with limited success, to find experimental conditions leading to one type of bonding or the other. In electrochemical systems, we have observed in simple isoquinoline systems[2] that steric hindrance around the bond being formed plays a strong role in product distribution. Furthermore, in simple isoquinoline systems (ref 2 as compared with this paper) and in 1-benzylisoquinolines[20] we have found that carbon–carbon dimers are formed predominantly but not exclusively in wet acetonitrile systems whereas the reverse is true in aqueous systems. From the arguments presented above, it is reasonable to assume that carbon–carbon dimer formation is a surface reaction. As a corollary, one might assume that carbon–oxygen–carbon dimer formation might take place away from the surface. If this were true, no stereochemistry would be involved and one should obtain both isomers of the carbon–oxygen–carbon dimer (C) owing to the two asymmetric centers when R is a substituent other than hydrogen. Although such isomers were not obtained when R = CH_3 (probably owing to the difficulties of the separation), they were obtained when R = benzyl[20] or when R = ethyl.[2] Thus, it seems fairly reasonable to assume that carbon–carbon dimers are surface products and carbon–oxygen–carbon dimers are not. Some type of adsorption, or lack thereof, which is controlled by solvent factors appears to be involved.

The mechanism of phenol coupling has generally been assumed[19,21] to be a radical coupling reaction. Radical intermediates have been observed by electron spin resonance and coupled products have been obtained. McDonald and Hamilton[22] have categorized the various radical processes which might take place, but they have also suggested that biosynthetic coupling processes may take place by concerted migrations of electron pairs. Ronlán and his co-workers[23] have made a detailed study of the electrochemical oxidation of phenols and have found that phenoxonium ions, as formed by loss of two electrons, seem to explain the results best. The phenoxonium ions attack a neutral molecule to form a coupled product[23a] or can react with a convenient nucleophile such as hydroxide to form hydroxydienones.[23b]

Since our isoquinoline substrates are quite similar to natural substrates and there should be a similarity between enzyme-surface reactions and electrode-surface reactions, we believe that the carbon–carbon coupling as shown in Figure 1 takes place by a two-electron migration process. The carbon–oxygen coupling (to form C) may take place by a similar two-electron migration, or it may be a radical coupling reaction.

Finally, we would like to suggest that stereoselective electrochemical reactions are more likely to take place under the following conditions. First, oxidations should be more promising than reductions since one has a possible electrostatic attraction between the positively charged anode and the type of electron-rich molecules which are likely to undergo oxidation in the first place. Furthermore, most of the molecules dealt with in organic chemistry have π electron systems in double bonds or aromatic rings[17] and oxygen or nitrogen atoms with their free pairs of electrons. Second, stereoselective reactions are more likely to take place with polyfunctional molecules where there are a number of binding sites spread over the molecule to help penetrate the double layer and to bring about a tight, highly oriented conformation on the electrode. Finally, of course, the molecule must be sufficiently complex that a preferred type of adsorption will take place.

Experimental[24] Section

Resolution of the Benzyl Ether of 1. A solution of 2.702 g of (−)-*O,O*-di-*p*-toluoyl-*d*-tartaric acid in 20 ml of ethanol was combined with 2.079 g of racemic benzyl ether[8] in 200 ml of ethanol. The crystalline precipitate which formed was collected by filtration and recrystallized from methanol to give 0.960 g (40%) of the tartrate of the *R* isoquinoline (as shown later) as colorless needles, mp 177–178°, $[\alpha]^{22}D$ −68.7° (c 1.0, methanol).

Anal. Calcd for $C_{39}H_{41}NO_{10}$: C, 68.36; H, 6.03; N, 2.04. Found: C, 67.97; H, 6.09; N, 2.01.

The mother liquor from the preceding experiment was evaporated to dryness, basified with 10% aqueous KOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (K_2CO_3), and evaporated to yield 1.1 g of pale yellow gum. This gum was dissolved in 100 ml of ethanol and treated with 1.35 g of (+)-*O,O*-di-*p*-toluoyl-*l*-tartaric acid dissolved in 10 ml of ethanol. The crystalline compound which formed was collected by filtration and recrystallized from methanol to give 1.1 g (46%) of the tartrate salt of the *S* isomer of the isoquinoline as colorless needles, mp 177–178°, $[\alpha]^{22}D$ +69.4° (*c* 1.0, methanol).

Anal. Found: C, 68.05; H, 6.05; N, 1.89.

The tartrates were decomposed by suspending them in benzene (3 g in 200 ml) and basifying with 10% aqueous KOH. The benzene layer was washed (H_2O), dried (K_2CO_3), and evaporated to yield a colorless gum. The *R* isomer was obtained in quantitative yield and had a rotation of $[\alpha]^{22}D$ +30.1° (*c* 1.0, methanol). The *S* isomer was obtained in 82% yield and had a rotation of $[\alpha]^{22}D$ −29.7° (c 1.0, methanol).

(*R*)- and (*S*)-1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1). The optically active benzyl ethers (1.0 g) were dissolved in 10 ml of ethanol, and 10 ml of concentrated HCl was added. The mixture was heated under reflux for 1.5 h and evaporated to dryness. The residue was basified with NH_4OH and extracted with $CHCl_3$. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to a residue which was crystallized from acetone to give the optically pure enantiomers of **1**. The *R* isomer was obtained in 58% yield as colorless needles: mp 182–183°; $[\alpha]^{22}D$ +29.2° (*c* 1.0, $CHCl_3$); ORD (c 1.0, $CHCl_3$) [ϕ] (λ, nm) +130° (370), 0° (335), −2320° (290), +1680° (260 sh), +1770° (245), +620° (240); ir (KBr) 2950 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.73 (s, 1, aromatic), 6.64 (s, 1, aromatic), 3.89 (s, 3, OCH_3), 3.57 (q, 1, J = 7 Hz, $CHCH_3$), 2.50 (s, 3, NCH_3), 1.37 (d, 3, J = 7 Hz, $CHCH_3$); NMR [$(CD_3)_2SO$] δ 6.57 (s, 1, aromatic), 6.53 (s, 1, aromatic), 3.72 (s, 3, OCH_3), 2.34 (s, 3, NCH_3), 1.22 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.76. Found: C, 69.37; H, 8.23; N, 6.89.

The *S* isomer was obtained in 67% yield as colorless needles: mp 182–183°; $[\alpha]^{22}D$ −29.8° (*c* 1.0, $CHCl_3$); ORD (*c* 1.0, $CHCl_3$) [ϕ] (λ, nm) −220° (370), 0° (335), +2380° (290), −1690° (260 sh), −1880° (245), −770° (240); ir and NMR spectra were identical with those of the *R* isomer.

Anal. Found: C, 69.30; H, 8.22; N, 6.48.

The *S* isomer of **1** (0.07 g) in 2 ml of methanol–dioxane (1:1) was added to 100 ml of diazomethane solution (derived from 3.0 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide). After 2 days at room temperature, the solvent was removed to yield a pale yellow

residue which was dissolved in benzene, washed (10% aqueous KOH followed by H_2O), dried (K_2CO_3), and evaporated to give (*S*)-(−)-carnegine (0.06 g) as a colorless oil, $[\alpha]^{22}D$ −28.0° (*c* 1.1, ethanol) [lit.[9] $[\alpha]^{22}D$ −24.9° (*c* 4.45, ethanol)]. The base was converted to a hydrochloride, mp 209–210° (lit.[25] 210–211°). In a similar manner the *R* isomer of **1** was methylated to give (*R*)-(+)-carnegine with an opposite rotation of and identical melting point with that of its hydrochloride.

Potassium Ferricyanide Oxidation of Racemic 1. Racemic **1** (750 mg, 3.6 mmol) in 30 ml of 8% aqueous NH_4OAc and 4 ml of 1 N H_2SO_4 was added, dropwise, to 2.3 g (9 mmol) of $K_3Fe(CN)_6$ in 75 ml of 8% aqueous NH_4OAc. The mixture was stirred for 1.5 h, basified with NH_4OH, and extracted with $CHCl_3$. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to yield a gum, 470 mg, which was separated by preparative TLC (methanol–NH_4OH, 95:5, on six layers 20 cm × 20 cm × 1 mm) into six bands. The adsorbent containing bands were visualized with uv light, removed from the glass plates, and eluted with methanol. The top band yielded, after crystallization from ether–hexane, 13 mg (1.8%) of the diether D, R = CH_3: mp 201–203° (lit.[5a] 200–205°); NMR ($CDCl_3$) δ 6.64 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.78 (s, 6, NCH_3), 1.58 (s, 6, C–CH_3); mass spectrum M^+ *m/e* 408 (calcd 408), 391 base peak.

The second band (from the top) yielded 53 mg of unchanged **1**.

The third band yielded 20 mg (2.8%) of the carbon–oxygen–carbon dimer, C, R = CH_3, as a powder, mp 97–100°, from ether–hexane. The material is unquestionably a mixture of stereoisomers, but was identical spectroscopically with the previously characterized material.[2]

The fourth band yielded 60 mg (8.3%) of the carbon–carbon dimer, **3**, mp 226–227°, identical spectroscopically in all respects with the previously characterized compound.[2]

The fifth band yielded 29 mg (4%) of the carbon–carbon dimer, **2**, as a glass, again identical spectroscopically with previously characterized material.[2]

The sixth band yielded 80 mg (11%) of the carbon–carbon dimer, **4**, mp 133–135° as crystallized from hexane–ether. The compound was identical spectroscopically with the previously characterized substance.[2]

Potassium Ferricyanide Oxidation of the Enantiomers of 1. Similar oxidations of the *R* and *S* enantiomers of **1** gave the results shown in Table I. The NMR spectra of the enantiomers of the four products were identical with those of the racemic products. However, the melting points were somewhat different. For the products of the *R* isomer, they follow: 212–213° for D, R = CH_3; 109–110° for the carbon–oxygen–carbon dimer C, R = CH_3; 164–165° for **3**; and 175–178° for **4**. For the products of the *S* isomer, they follow: 209–211° for D, R = CH_3; 111° for C, R = CH_3; 162–165° for **3**; and 176–178° for **4**. Since **2** requires isoquinolines with opposite configurations at C-1, it could not be formed from the enantiomers and was not, in fact, observed.

Electrooxidation of Racemic 1 and Its Enantiomers in Excess Sodium Methoxide.[26] Racemic **1** (600 mg, 2.9 mmol) was dissolved in 115 ml of 0.1 M $NaOCH_3$ in methanol and evaporated to a slightly colored gum. This gum was dissolved in a mixture of 300 ml of CH_3CN and 10 ml of H_2O, and 4.0 g of tetraethylammonium perchlorate was added. The solution was cooled to 5–10° and oxidized in a two-compartment cell using a graphite felt anode (6 × 20 cm),[27] a platinum cathode, and an SCE reference electrode.[28] The compartments were separated by a fritted glass disk; nitrogen was continuously bubbled through the cooled mixture; and the potential was controlled at +0.04 V. The initial current of 35 mA fell to 15 mA over a period of 4 h, when TLC showed that very little starting material remained. The solution was removed from the cell, and the felt electrode was washed with methanol.[29] The reaction mixture and washings were acidified with HCl and concentrated to a pale brown gum which was subsequently basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. Preparative TLC was used as described previously to separate the mixture into starting material (63 mg), carbon–oxygen–carbon dimer (42 mg, 6.8%), and **3** (413 mg, 68.9%). Careful TLC of the crude reaction mixture as well as the various bands as they were removed failed to show the presence of either **2** or **4**. The yields as corrected for starting material are given in Table I.

Oxidations of the enantiomers of **1** under identical conditions gave the results in Table I. The melting points of the products were the same as those found in the ferricyanide oxidations. The optical properties of the products are as follows: for C, R = CH_3, from the *R* isomer, $[\alpha]^{22}D$ +12.0° (*c* 0.11, CH_3OH); for **3** as derived from the *R* isomer, $[\alpha]^{23}D$ −17.8° (*c* 1.0, CH_3OH), ORD (*c* 0.02, C_2H_5OH) [φ] (λ, nm) 0° (330), +80° (306), −1280° (292), +640° (271), +350° (254), +470° (246), +260° (240); for C, R = CH_3, from the *S* isomer, $[\alpha]^{22}D$ −11.2° (*c* 0.25, CH_3OH); for **3** as derived from the *S* isomer, $[\alpha]^{23}D$ +16.9° (*c* 0.25, CH_3OH), ORD (*c* 0.029, C_2H_5OH) [φ] (λ, nm) −100° (330), −270° (306), +1370° (292), −1000° (271), −650° (254), −800° (246), −600° (240).[30] The optical properties of D, R = CH_3, are discussed elsewhere.[7]

Electrooxidation of Racemic 1 under Other Conditions. The oxidations in one compartment are self-explanatory.[28] The sodium salts[28] were prepared from equimolar amounts of **1** and $NaOCH_3$ and were oxidized in CH_3CN–H_2O–TEAP as described above. In this case the drop-off of current was almost complete (38 to 2 mA) during the experiment. The reactions were stopped when the current fell to 2–5 mA or when TLC showed that starting material was essentially gone. The neutral reactions were carried out in the same system. In the neutral reactions, the potential was increased from +0.24 to +0.36 V to maintain the current at 31 mA during the 6.5-h experiment (on 400 mg of **1**). The hydrochloride reactions were carried out in the same CH_3CN–H_2O–TEAP system on salts prepared with HCl gas in ether. A much higher potential was required as expected,[28] and yields were poor. The excess acid reactions were carried out in 0.1 N HCl. In all cases, the products were isolated as described, and the results are given in Table I.

Equilibration of Isomers 2, 3, and 4. Air was bubbled through a mixture of **3** (150 mg), 200 ml of MeOH, and 750 mg of 10% Pt on carbon[31] for 3 days. The catalyst was removed by filtration, and the solvent was evaporated to a brownish residue. The residue was chromatographed by MeOH–12 N HCl (10:1), and the major zone was isolated to give a crude mixture of 3,4-dihydroisoquinolinium salts. The mixture (43 mg) in 50 ml of MeOH was treated with 100 mg of $NaBH_4$ and heated to reflux for 30 min. The mixture was acidified, concentrated to dryness, and partitioned between $CHCl_3$ and basified (NH_4OH) H_2O. The $CHCl_3$ extract was washed (H_2O), dried ($MgSO_4$), and evaporated to give 22 mg of a colorless gum. Chromatography on shaped layers and direct comparison by chromatographic "spiking" showed that the gum consisted of the three isomers **2**, **3**, and **4**.

Acknowledgment. In addition to the financial support previously acknowledged, the authors would like to thank Professors S. J. Huang and J. T. Stock of this Department for their many helpful suggestions and Dr. Richard Hallcher for carrying out the equilibration studies.

Registry No.—*rac*-**1**, 19641-12-4; (*R*)-**1**, 35048-35-2; (*S*)-**1**, 35053-29-3; *rac*-**1** benzyl ether, 57550-06-8; (*R*)-**1** benzyl ether, 57527-65-8; (*S*)-**1** benzyl ether, 57527-66-9; (*R*)-**1** benzyl ether tartrate, 57527-67-0; (*S*)-**1** benzyl ether tartrate, 57527-68-1; **2**, 57550-07-9; *rac*-**3**, 57550-08-0; (*SS*)-**3**, 35053-14-6; (*RR*)-**3**, 35068-21-4; *rac*-**4**, 57550-09-1; (*SS*)-**4**, 35048-36-3; (*RR*)-**4**, 35048-37-4; **5**, 57550-10-4; C (R = CH_3), 19626-08-5; *rac*-D (R = CH_3), 57605-21-7; D (R = CH_3) from (*R*)-**1**, 57550-05-7; (−)-*O*,*O*-di-*p*-toluoyl-*d*-tartaric acid, 32634-66-5; (+)-*O*,*O*-di-*p*-toluoyl-*l*-tartaric acid, 32634-68-7.

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(26) This experiment will be described in detail since it was found to give the best yields.
(27) WDF graphite felt, Carbon Products Division, Union Carbide Corp., New York, N.Y.
(28) For general cell design see ref 2 and G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, J. Electrochem. Soc., 116, 219 (1969).
(29) This is generally done by shredding the electrode in a Waring Blendor with methanol followed by suction filtration.
(30) The ORD curves for these compounds and for the enantiomers of 1 were not corrected for zero lines and are therefore not exactly equal and opposite. A better criterion for purity is probably the more accurately measured rotations at the D line of sodium.
(31) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, p 151.

The Chiroptical Properties of Bistetrahydroisoquinoline and Polycyclic Biaryl Derivatives[1]

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The ORD and CD spectra are described for the atropisomers of 8,8′-bis-1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (2), which were prepared by the electrochemical and chemical oxidation of (*S*)-(−)-1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1). The anticlinal isomer **2a**, mp 164–165°, probably has the (1*S*,1′*S*,biphenyl-*S*) configuration and gives CD curves with moderate Cotton effects while the curves of the synclinal isomer **2b**, mp 176–178°, of (1*S*,1′*S*,biphenyl-*R*) configuration vary more significantly with pH. A third product, which may result from cyclization of one of the atropisomers, probably has hexacyclic structure 3b and is assigned the *S* configuration at both chiral centers and the *R* configuration (*P* helicity) of the biaryl chromophore based on the signs of the high-intensity Cotton effects.

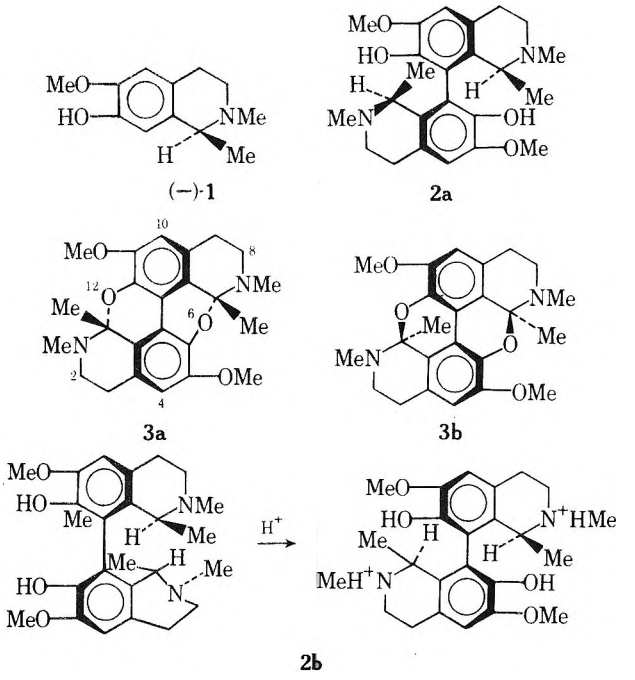
The helicity of ortho-substituted biphenyls has been correlated with chiroptical properties [circular dichroism (CD) and optical rotatory dispersion (ORD)] by Mislow and his collaborators.[2–4] These workers observed that the nature of the substituents had profound effects on the chiral properties, but the inherently dissymmetric chromophore dominated the ORD and CD curves. The ortho,ortho′ substituents were then cyclized to yield bridged biphenyls of known[4a] absolute configuration and helical sense. The size of the ring and nature of the bridge determined the angle from coplanarity (angle of torsion) of the benzene rings. When the bridge stabilized the helicity and lacked additional elements of dissymmetry, the sign of the strongest Cotton effect could be related to the absolute configuration or sense of twist of the molecule.[4b] Since these first observations were made, a number of investigators have discussed the correlation of the ORD and CD spectra in a variety of systems with the helicity of the chromophore.[5,6]

The study of the chiroptical properties of biaryl derivatives produced by coupling of phenolic tetrahydroisoquinolines was undertaken to ascertain the stereochemical consequences of inducing helicity in the biaryl moiety. Since the starting monomeric species possessed a single chiral center at C-1, the dimeric products contain an additional center of dissymmetry, the biaryl, whose helical sense may be predicted from the signs of the circular dichroism Cotton effects. A doubly bridged biaryl also resulted from the electrochemical oxidation, and its helicity may be deduced from ORD and CD measurements which would suggest some steps in the mechanism for its formation.

Bobbitt and co-workers have synthesized chiral biaryl derivatives by the methods described in the accompanying paper.[7] The configurations were assigned from NMR evidence, and confirmation of the assignments was sought by the chiroptical methods described below.

The compounds were prepared by the electrochemical and chemical dimerization of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(±)-1], and its enantiomers.[7,8] Bobbitt and co-workers[9] have shown that a bond is formed at the 8 positions, ortho to the hydroxyl

group. Rearomatization produces the biaryl **2**. The presence of the substituents at the chiral center at the ortho,ortho′ positions creates steric interference to rotation about the biphenyl bond and adds a new element of dissymmetry. As a result two biaryls, **2a** and **2b**, result from the coupling



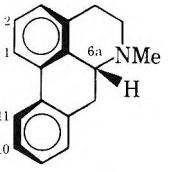
of a single enantiomer [(*S*)-(−)-**1**], but the product has a new element of dissymmetry (the helicity of the biaryls) which results in the formation of two diastereomers which are atropisomers[10a] and have been called *rotamers*.[8] A second pair of diastereomers would arise from the (*R*)-(+)-**1** enantiomer.[10b] A recent report cited evidence for the existence of diastereomeric conformations in solution for an enantiomer of a chiral biphenyl.[10c]

If rotation about the bond joining the aromatic rings permits the ortho substituents to pass each other, the rotamers will be interconverted. This energy barrier is probably high because of the size of the chiral ortho substituents. A number of conformations are possible, but those derived from (*S*)-(−)-**1** which have the probable minimal nonbonded interactions have the left-handed helical sense of the biphenyl as shown in **2a** and **2b**. Both enantiomers were studied for all compounds, but the discussion will concern the products from the (*S*)-(−)-**1** series. Data from the enantiomeric series derived from (*R*)-(+)-**1** will be used in some examples with appropriate sign changes.

The third biaryl compound isolated from the oxidative coupling reactions resulted most likely from cyclization of the rotamers. The phenolic oxygen formed a bridge to the 1 position of **2** which created an aminoketal type of functional group. Since both hydroxyl groups produced the ethereal bonds, the doubly bridged biphenyl 5,11-dimethoxy-6a,12a-dimethyl-1,2,3,6,6a,7,8,9,12,12a-decahydro-6,12-dioxa-1,7-diazadibenzo[*def,mno*]chrysene (**3**) was formed.[7]

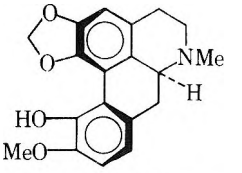
The configurations of the products of the phenolic coupling can be derived from that of the starting material whose rotation, (+) or (−), is specified by the observed rotation at 589 nm in chloroform solution. When (*S*)-(−)-**1** is coupled with itself by a phenolic oxidation process, the products **2** retain the *S* configuration at the asymmetric carbon atoms, but the configuration of the biphenyl will be *R* in one isomer and *S* in the other.[11] The assignment of configuration to the two products isolated in this reaction is complicated by the fact that each isomer has syn and anti conformations. Because of the dissymmetry produced by the chiral carbon centers at C-1 and C-1′ of the tetrahydroisoquinoline moieties, the nonbonded interactions destabilize one conformer appreciably leading to the predominant structures **2a** and **2b**. The anticlinal[11b] isomer **2a** has thg (1*S*,1′*S*,biphenyl *S*) absolute configuration, while the synclinal[11b] isomer **2b** has the (1*S*,1′*S*,biphenyl *R*) configuration. On the basis of NMR data the racemate melting at 226–227° was assigned the anticlinal structure **2a** and its enantiomer.[8] The CD data discussed below will support this assignment.

The helical sense of **3** is determined by the absolute configuration at the asymmetric carbons, 6a and 12a. A similar observation was made by Shamma[12] in the case of the aporphine alkaloids **4** and **5**. When the bridge between the biphenyl carried the *R* configuration (C-6a in aporphine **4**), the biphenyl moiety could only achieve a left-handed twist. The absolute configuration of the biphenyl moiety of **4** is also *R* by the Cahn–Ingold–Prelog nomenclature system[11] when no other substituents are present at C-1 or C-11, while that of **5** would be *S*. A more satisfactory terminology which is not dependent on substituents but only on the sense of twist is to describe **4a,b** as having *M* helicity and **5** with *P* helicity.[10]



4a, nuciferine, OCH_3 at C-1, C-2

4b, apomorphine dimethyl ether, OCH_3 at C-10, C-11



5, bulbocapnine

The stereochemistry of the cyclized product **3** cannot be assigned unless the mechanism by which cyclization occurs is known or the configuration at the asymmetric carbons can be determined by other methods. The cyclization of **2a** would yield **3a** by retention of configuration where oxygen replaces hydrogen but would yield **3b** only by inversion at all chiral centers. Hence, **2b** or its precursor must lead to **3b**. As long as the pathway yields an optically active product, the configurations at both carbons must be the same and will determine the helical sense of the molecule. This results from the same strains Shamma found for the aporphine alkaloids.[12b] In **3a** this is a left-handed screw sense, *M* helicity, and **3b** has the right-handed or *P* sense.[10] A correlation of the helical sense with the signs of the Cotton effects of chiral molecules has been discussed from several theoretical approaches by Brewster[13] and, more recently, by Hug and Wagnière.[6] Mason et al. have assigned absolute configurations to open biphenyls,[5b] binaphthyls,[5b] and bianthryls[5c,14] on the theoretical treatment of CD results. Utilization of the rules formulated for biphenyls by Hug and Wagnière[6] leads to the proposition that the helical sense of the product **3** obtained from (*S*)-(−)-**1** is probably *P*. This helicity must result from inversion of configuration at the asymmetric carbons and produce the 6a*S*,12a*S* absolute configuration shown in **3b**.

Experimental Section

Absorption spectra were recorded on the Cary 15 or a Beckman DK-2A with 95% ethanol as solvent. Measurement at 27° of the ORD and CD spectra was accomplished with the Cary 60 equipped with a 6001 circular dichroism attachment. The CD spectra were recorded in 95% ethanol and concentration and path length were varied by diluting the concentrations given in the figures or by using cells of light path 1.0, 0.1, or 0.05 cm. The solutions showed pH about 5. After the spectrum was recorded, a drop of concen-

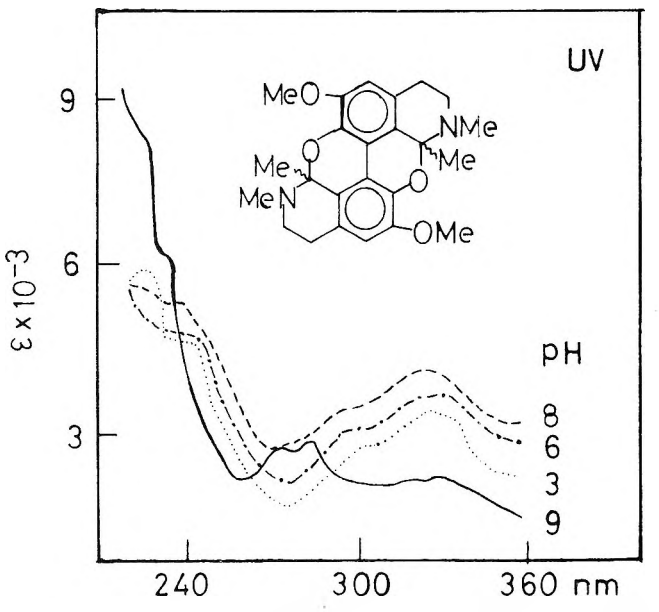


Figure 1. Uv spectra of 3 in 95% ethanol: —, fresh solution and pH 9; ····, pH 3; - · -, pH 6; - - -, pH 8. The pH may be changed in either direction with duplication of curves.

trated HCl was added to pH 2, and the spectrum was remeasured. Neutralization with solid KOH gave solutions whose spectra appeared essentially identical with the original curves (pH 8). Additional KOH was added to obtain strongly basic solutions (pH 10). Reported spectra were recorded at least twice and by different analysts with agreement in wavelength and sign and 10% maximum variation in amplitude. The CD spectra and some ORD curves of both enantiomers were obtained, and the figures show curves for only the enantiomer comparable to or derived from (*S*)-(−)-**1**.

The compounds were obtained as previously described[7] by the electrochemical or chemical dimerization of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(±)-**1**] and each enantiomer of **1**. Purity of the products was confirmed by measuring spectra of both enantiomers of each structure. The absolute configuration *S* was assigned to (−)-**1** on the basis of chemical correlation.[8]

Results and Discussion

Uv Spectra. The electronic spectra of biphenyl derivatives[15] usually show a large band at about 250 nm which has been called the conjugation band, one or more weak bands at longer wavelength characterized as the ^1L_b band in Platt's notation,[16] a band at ca. 230 nm which may be the ^1L_a band, and the bands at 220 nm and below corresponding to the ^1B bands of benzene. The ^1L_b and ^1L_a bands of biphenyl apparently overlap in a broad 250 nm conjugation band.[15] The substitution of hydroxyl or ether groups on the aromatic ring causes red shifts.[17] The combination of two tetrahydroisoquinoline moieties into the biphenyl structure was expected to give spectra similar to that of **1** plus the intensive biphenyl conjugation band. The hexacyclic product **3**, which is formally a doubly bridged biphenyl, should also absorb at 250 nm as well as show phenolic bands.

The complex spectra of the cyclized product **3** shown in the study of pH variation (Figure 1) contrasted with the relatively featureless spectra of the monomer **1** and dimers **2** (Figures 2–4). The spectra of **1** and **2** showed the ^1L_b band of monomethylated catechol at 288 nm, which is the only significant peak at long wavelength in neutral or acid media. A shoulder at 255–260 nm which is not present in the spectra of **1** appeared on acidification, indicating further biphenyl interaction.

In contrast to these very simple spectra, **3** on dissolution in alcohol (pH 8.5–9) absorbed ($\epsilon \sim 10^4$) at 330, 283, 273, and 240 nm with a shoulder at 317 nm (Figure 1). The

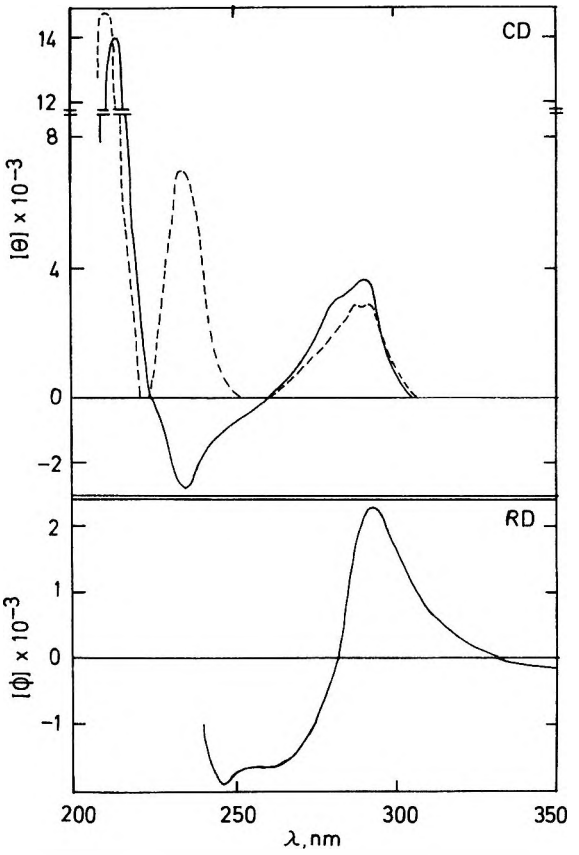


Figure 2. CD and ORD of (*S*)-(−)-**1**, c 0.417 mg/ml, 95% ethanol (—) and CD (- - -) in acidified ethanol.

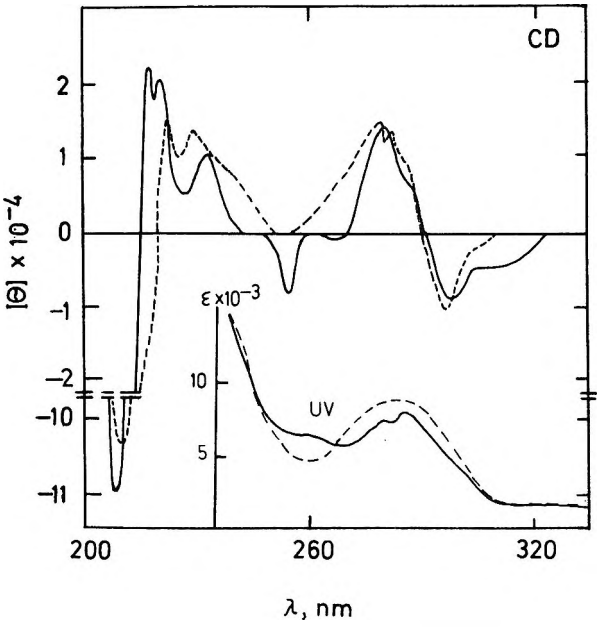


Figure 3. CD and uv of *SS* rotamer A (**2a**), c 0.162 mg/ml, 95% ethanol (- - -) and in acidified ethanol, pH 2 (—).

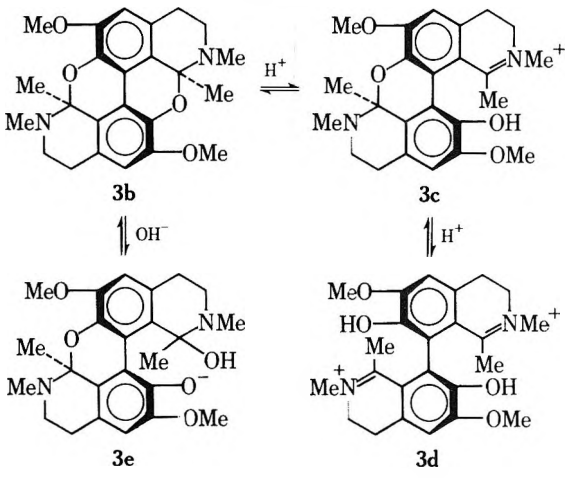
bands changed in intensity and structure on addition of acid and showed variation in extinction coefficient with pH 1–8 which precluded equilibria studies.[18] At pH 9 the spectrum changed, resembling that of the original solution. Acidification of this solution restored the curve at pH 3 with only a 5% loss of intensity in the 330-nm band and no other change.

The absorption of the biphenyl chromophore at 240–245 nm was constant from pH 1 to 6, increased from pH 6 to 8, and was lost or hidden under the strong 230-nm band at pH 9. Since the conjugation band is expected to be inde-

pendent of pH, it was sought and found to be strong in the CD spectra (vide infra), and the wavelength did not change with pH. The presence of two bands, 330 and 300 nm, may indicate exciton splitting of the ^1L_b band.

The curve of **3** obtained initially in alcohol very likely indicates only the molecular species which undergoes ring opening in both acid and base. An equilibrium shown in Scheme I is consistent with the uv spectra. In acid, the

Scheme I



ring-opened structures **3c** and **3d** have decreased conjugation of the biphenyl because the methyl group at C-1 is coplanar with the benzene ring. Thus the absorption decreases at 240, 300, and 330 nm with decreasing pH. Chirality is retained, however, because of the interference to free rotation. Basification leads to **3e** and comparison of the spectrum at pH 9 with that of the original solution showed a similar curve which has a broadened band in the 300–340-nm region, possibly due to phenoxide absorption.

The small but possibly significant differences in the uv curves of the atropisomers **2** and the variation with pH shown by **3** suggested that the removal of some overlapping absorptions and presentation of signed maxima in the CD spectra should permit clarification of the uv spectra. In addition, the signs of the bands should test the validity of the conformational arguments and suggest the helicity of the twisted biphenyls in **2a, 2b,** and **3**.

CD Spectra. The starting material (*S*)-(−)-**1** has positive ^1L_b Cotton effects at 290 and 280 nm (Figure 2). Snatzke and Ho[19] assigned *M* helicity to the heterocyclic ring in a tetrahydroisoquinoline having oxygen substituents at C-6,7 if the compound gave a positive ^1L_b Cotton effect. This assignment requires the 1-methyl substituent to assume an axial conformation which is plausible from examination of molecular models. A negative Cotton effect at 236 nm resulted from the ^1L_a transition, and the ^1B Cotton effect at 212 nm was positive. The acidified spectrum showed similar ^1L_b and ^1B bands, but the ^1L_a band inverted to a positive ellipticity at 233 nm.

Dimerization should add the biphenyl bands to the spectra and produce a red shift of other bands. The anticlinal conformation of **2a** is consistent with the isomer, mp 226–227°, which showed very similar spectra in neutral and acidic solutions. Suzuki[15] found that the dihedral angle of biphenyl (23°) was enlarged to 70° with ortho,ortho′ disubstitution, and the angle in **2a** may be even larger. Protonation of the diamine should not appreciably change the conformation or the CD spectra. The CD curves of **2a** in both neutral and acidic media (Figure 3) gave one band with a negative sign at 300 nm and a positive maximum at 284 nm which may result from exciton splitting of the ^1L_b band. An

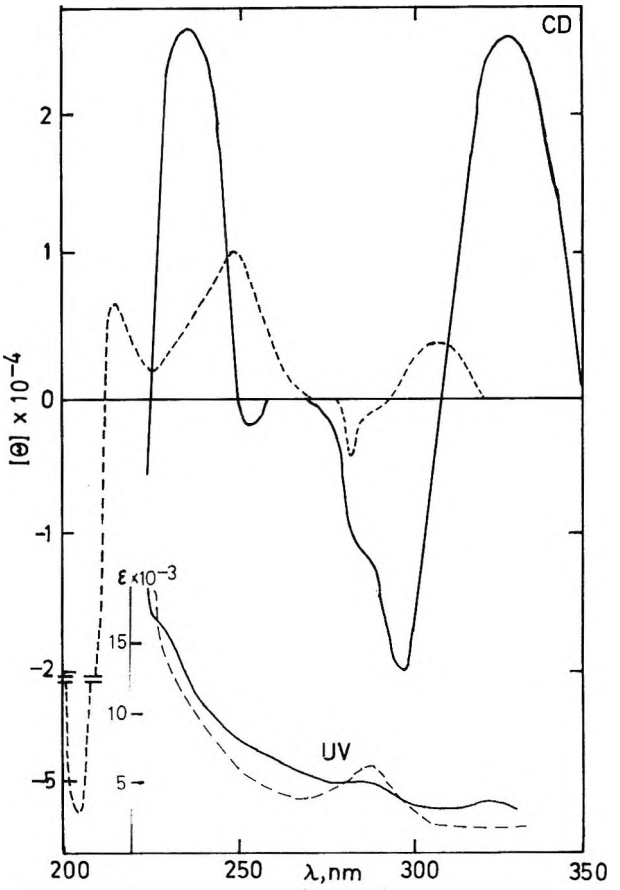


Figure 4. CD and uv of *SS* rotamer B (**2b**), c 0.042 mg/ml, 95% ethanol (- - -) and in acidified ethanol, pH 2 (—).

overlapping band at 279 nm increased the breadth of the positive half of the bisignate band. The second atropisomer **2b** showed a negative, single Cotton effect at 284 nm (Figure 4) with no splitting. Acidification of the solution, however, gave a striking increase in ellipticity and the appearance of a long wavelength bisignate Cotton effect. The band was shifted to the red with maxima at 330 and 300 nm, the former being positive.

Use of the ^1L_b traniition for assigning absolute configuration and helical sense to twisted biaryls has been calculated for a variety of systems since Kuhn[20] first attempted to determine the absolute configuration of 2,2′-diamino-6,6′-dimethylbiphenyl. The data were recently reexamined by Mason et al.[5b,14] along with the studies of binaphthyls and bianthryls. The results of the theoretical treatment were consistent with the known configurations. Hug and Wagnière proposed[6] that the helicity of a biaryl which shows an exciton split of the ^1L_b Cotton effect can be correlated with the sign of the CD band. According to their rules, a bisignate Cotton effect with a positive long-wavelength maximum resulting from B-type symmetry of the electronic transition correlates with a biphenyl of *P* helicity. Exact identification of this transition, its symmetry type, and characterization as exciton splitting are essential. Assuming that these criteria are applicable to the spectra of **2a** (Figure 3), the negative 300 nm and positive 280 nm exciton split Cotton effect indicates *M* helicity which was also predicted by Bobbitt et al.[8] from the NMR data and absolute configuration at C-1 and C-1′. If the acidified spectrum of **2b** (Figure 4) also meets the criteria, the long-wavelength positive maximum of the exciton split ^1L_b band shows that **2b** has *P* helicity in acid. Since **2b** probably has the syn relationship of the amino groups in neutral solution, diprotonation should cause repulsion of the ammo-

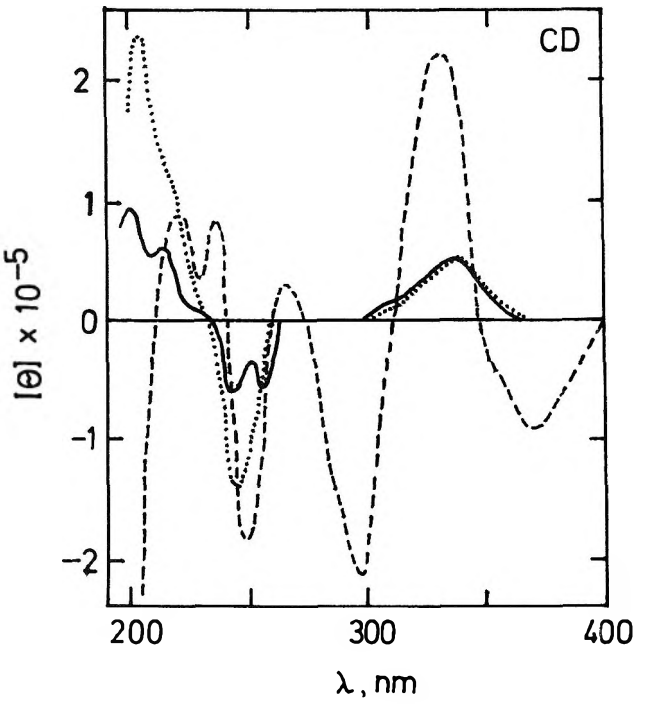


Figure 5. CD of **3** prepared from (*S*)-(−)-**1** at pH 2 (- - -), pH 5–8 (—), and pH 10 (· · · ·), *c* 0.076 mg/ml 95% ethanol.

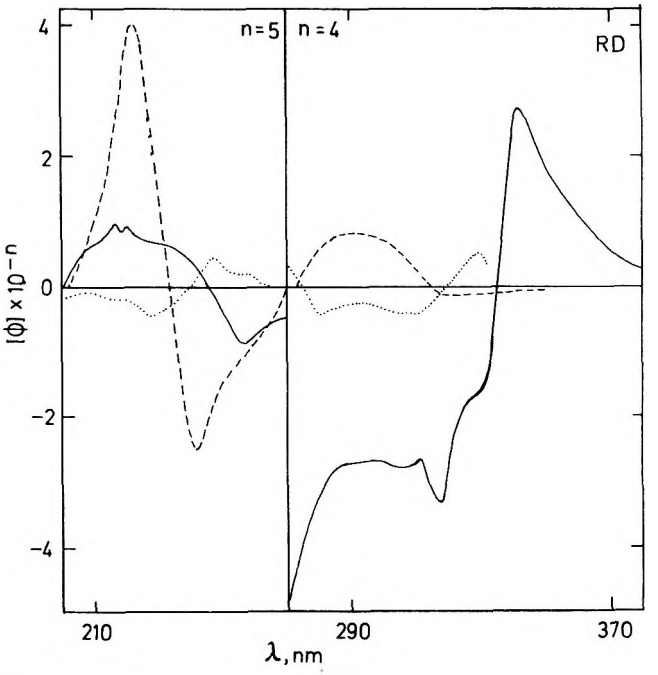


Figure 6. RD in 95% ethanol of **3** prepared from (*S*)-(−)-**1**, *c* 0.0676 mg/ml (—), (*S*)-(+)-bulbocapnine (**5**), *c* 0.159 mg/ml and adapted from ref 23 (· · · ·), and (*R*)-(−)-apomorphine dimethyl ether hydriodide (**4b**), *c* 0.247 mg/ml (- - -).

nium ions and open the biphenyl to the anticlinal conformation. This is consistent with the *P* helicity of the salt which would be predicted from the knowledge of the absolute configuration and NMR data.[8]

The identification of the biaryl ^1L_a band is not certain. Verbit[21] proposed a CD bandwidth criterion for characterizing this band in benzene derivatives. Resolution of these curves on a Du Pont Model 310 instrument eliminated some bands on this basis but did not clearly identify the ^1L_a band in either compound.

The very strong bands at 200–210 nm in the spectra of **2** which may be the result of the ^1B_b transition were proposed by Ferris et al.[22] as diagnostic for helicity of some bridged biphenyls. Theory suggested[5c] that they should have the same sign as the ^1L_b Cotton effect. In this case, both **2a** and **2b** have negative Cotton effects at about 210 nm in alcohol, but the acidic solution of **2b** was not readable in this region. Use of this band may become possible with further developments in instrumentation.

The CD spectra of **3** prepared from (*S*)-(−)-**1** are quite complex (Figure 5), but the ^1L_b transition gave a positive, unsplit Cotton effect at 318 nm with a shoulder at 310 nm. Acidification produced a very strong, bisignate Cotton effect with the positive maximum at 330 nm and the negative maximum at 298 nm. A longer wavelength negative Cotton effect appeared at 370 nm which may be a charge transfer band. The positive sign of the exciton split band at 330 nm requires assignment of *P* helicity to **3** according to the rules of Hug and Wagnière.[6] The biphenyl conjugation band at 244 nm was almost constant with pH change but became stronger and shifted to 250 nm in base. It remained negative at all pH values. The similarity of the spectra in acid medium of **2b** and **3** prepared from (*S*)-(−)-**1** is striking, especially in the long-wavelength region (Figures 4 and 5). The rules of Hug and Wagnière[6] thus demand the assignment of *P* helicity to both compounds in acid solution. With *P* helicity, **3** must have the absolute configuration shown in **3b**, i.e., 6a*S*,12a*S*.

The aporphine structures **4** and **5** were expected to be models for **3**, but there were critical differences. The aporphines have a two-carbon bridge between the benzene rings while **3** has an oxygen–carbon bridge. The helicity is governed in both systems, however, by the absolute configuration of the C-6a (and C-12a in **3**) atom and its substituents. Thus knowledge of one leads to assignment to the other center. The oxygen substituents of the aromatic rings are on opposite sides of the rings (i.e., anti) and thus opposite to the syn arrangement in the aporphines which probably prevents the aporphines from being satisfactory models for **3**. The similarity of the RD curves (Figure 6) of **3** prepared from (*S*)-(−)-**1** and the alkaloid nuciferine[23] (**4a**) led to the initial assignment of configuration based on *M* helicity.[1b] The conjugation bands are strong and negative, that of **3** being at slightly longer wavelength than that of **4a**. The ^1L_b bands in the aporphines have relatively low amplitudes and are of questionable value in assignment of configuration.[23] Since **3** gave opposite signs of the ^1L_b (positive, 320 nm) and conjugation (negative, 245 nm) bands, no assignment was possible based only on model aporphine compounds in which these bands have the same sign [e.g., bulbocapnine (**5**), positive, 320 and 240 nm]. Application to **3** of the method Mason used[24] for boldine was also inapplicable because of the structural differences. In view of the strength of the ^1L_b exciton split transition, the assignment of *P* helicity to **3** based on the rules of Hug and Wagnière[6] seems plausible. It is certain that the aporphines are not satisfactory models for this compound, and an analysis of **3** would be desirable on a theoretical basis since it is a rare example of an anti oonfiguration of the oxygen in a bridged bicyclic analogous to the aporphine structure.

The mechanism by which (*S*)-(−)-**1** is converted to **3b** is not established, but the hydrogen at C-1 must be removed initially as the atom or ion causing loss of chirality at the carbon center. The chirality of **3** would, therefore, be determined by the twist of the biphenyl system in the intermediate. If **2a** is the precursor to **3b**, this requires both a change in the twist of the biphenyl and formation of the O–C bond leading to the *S* configuration. This is an unlikely pathway. If **2b** or a precursor to **2b** is the intermediate leading to **3b**, only the latter change is required which

would give the *S* configuration at C-6 and C-12 of **3** and would retain the *P* twist of the biphenyl.

Acknowledgment. The author is grateful for the technical assistance of Mr. Ingo Hartmann in this study. Appreciation is due Professor James M. Bobbitt for supplying the compounds and for enlightening discussion. She is most appreciative for the suggestions of the referees and discussion with Dr. A. Moscowitz, but she alone is responsible for the conclusions described herein. The author is grateful to the University of Virginia Chemistry Department for their courtesy during the preparation of this manuscript.

Registry No.—(−)-**1**, 35053-29-3; **2a**, 35053-14-6; **2b**, 35048-36-3; **3b**, 57550-05-7.

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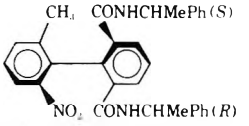

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Cyclization of Unsaturated Hydroxylamine Derivatives[1]

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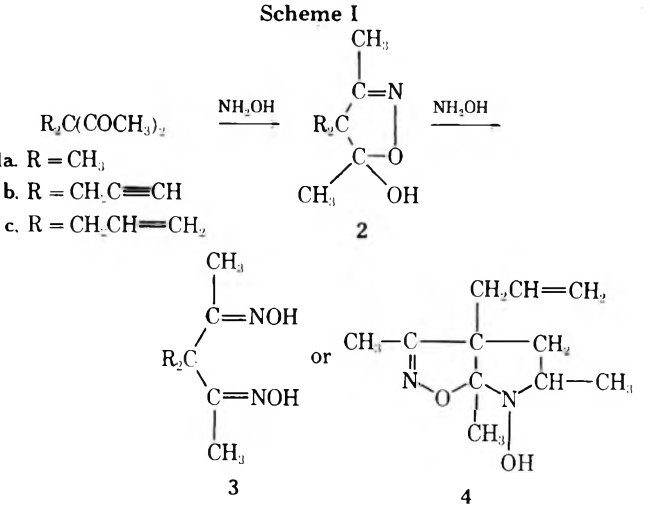
Reaction of the α-allyl β-diketones **5** with excess $HONH_2$ yielded the bicyclic pyrrolidine derivatives **7** in which a new N–C bond had been formed by cyclization of an intermediate *N*-(4-pentenyl)hydroxylamine **14**. Study of conversion of the *N*-alkenylhydroxylamine **20** to form the cyclic hydroxylamine **24a** and the electrochemical oxidation of hydroxylamines **20**, **24a**, and **31** suggested that these ring closures **14** → **15** occur by a radical chain process involving an intermediate nitroxide radical **37**.

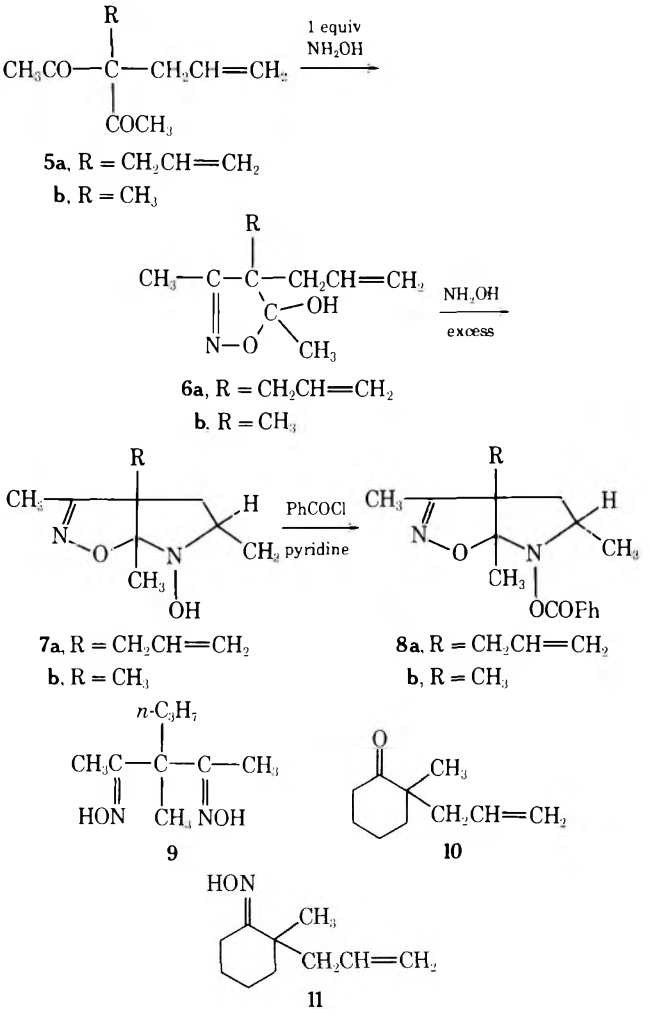
An earlier investigation[3] of the reaction of 3,3-disubstituted 2,4-pentanediones (**1** Scheme I) with excess hydroxylamine had provided the curious observation that although the dimethyl derivative **1a** could be converted either to the isoxazoline **2** or the dioxime **3**, the dipropargyl derivative **1b** was remarkably resistant to conversion beyond the isoxazoline stage **2**. In seeking further information relating to these observations, reaction of the diallyl derivative **1c** with excess hydroxylamine was also examined. Again, formation of an isolable dioxime **3** was unfavorable; treatment of the isoxazoline **2** (R = allyl) with hydroxylamine under vigorous conditions led to the formation of an unexpected isomeric substance subsequently shown to have the structure **4**. In this paper we describe the evidence on which the assignment of structure **4** is based and also described are our observations pertaining to the mode of formation of this substance.

Two 1,3-diketone substrates, **5a** and **5b** (Scheme II),

Scheme I



Scheme II

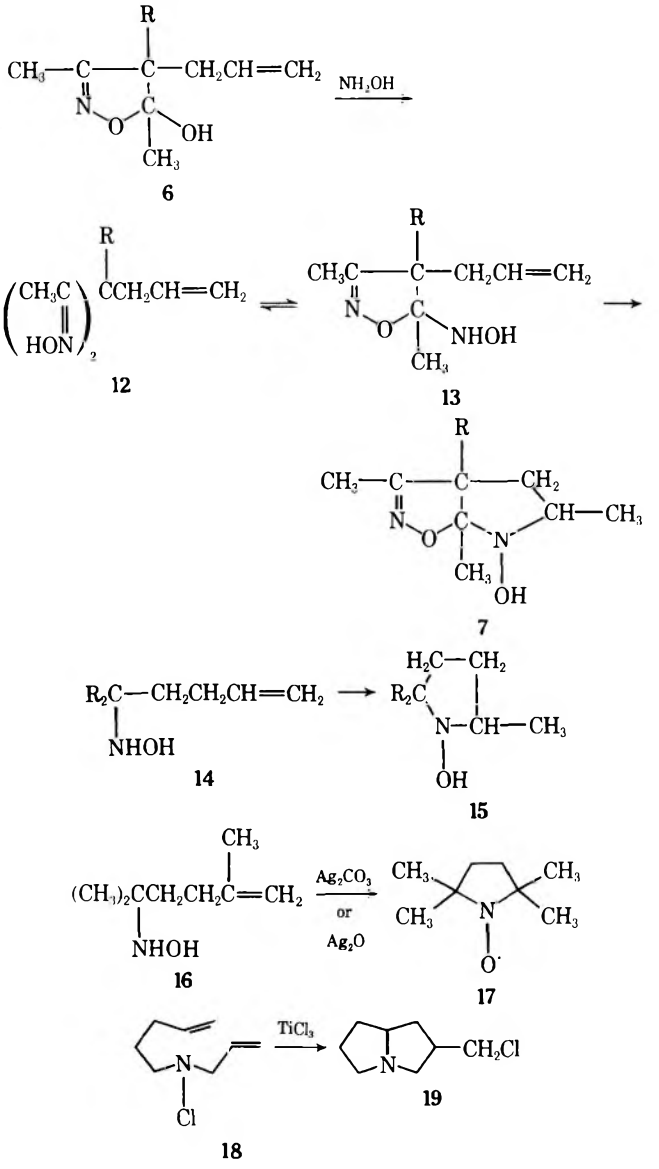


were selected for further study. Reaction of either of these products with 1 molar equiv of NH_2OH (from $HONH_3Cl$ + NaOAc) in aqueous dioxane or aqueous EtOH afforded the corresponding isoxazoline **6** that was isolated and fully characterized. Reaction of either the diketone **5** or the corresponding isoxazoline **6** with excess NH_2OH in refluxing aqueous EtOH or refluxing aqueous dioxane for a period of 6–24 h produced the bicyclic products **7**. In each case, the predominant product was one stereoisomer of structure **7**; from the reaction with the diallyl ketone **5a**, a second unidentified minor product, isomeric with **7a**, was isolated that appears to be a structural rather than a stereoisomer of **7a**. From reaction with the diketone **5b**, two stereoisomers of structure **7b** and a third minor component identified as the dioxime **9** were also isolated. This saturated dioxime **9** is not further altered by the conditions of the reaction and, consequently, is not an intermediate in the formation of the bicyclic hydroxylamine **7b**. When these same reaction conditions were applied to the α-allyl ketone **10**, only the expected oxime **11** was isolated indicating that the ring-closure reactions to form products **7** were not characteristic of prolonged reaction of simple α-allyl ketones with NH_2OH.[4]

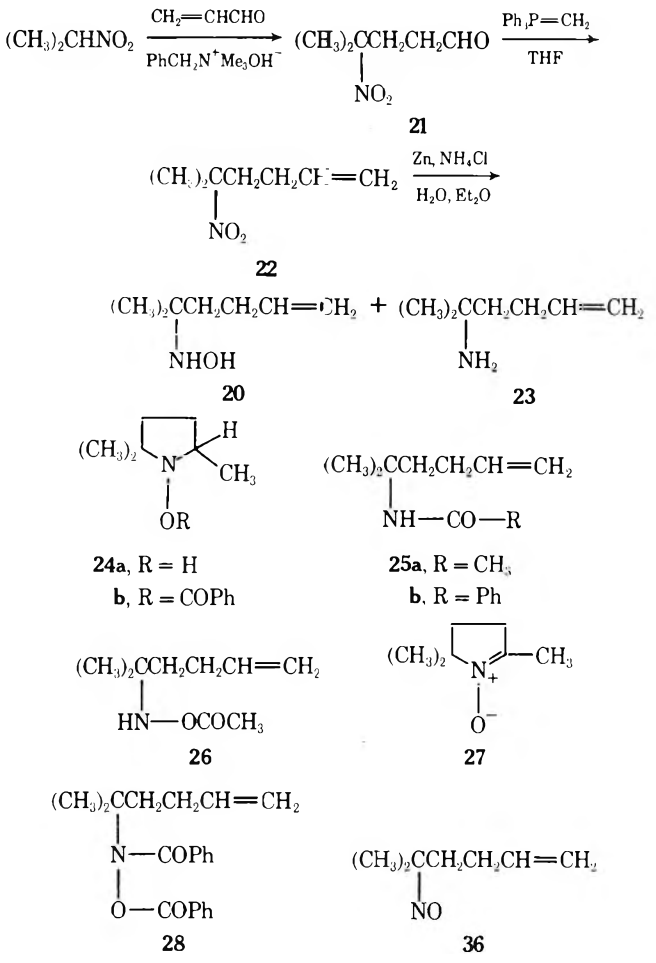
The spectroscopic properties (see Experimental Section) of the cyclic hydroxylamine derivatives **7** and the corresponding *O*-benzoates **8** taken with the structures of the starting materials **5** and the intermediates **6** served to define completely the structures **7**. It was therefore probable that the reaction pathway involved in these transformations was the transformation of the isoxazoline **6** (Scheme III) to the unsaturated hydroxylamine **13** (which is presumably in equilibrium with the dioxime **12**) followed by closure to cyclic product **7**. The unusual reaction in this sequence is the final cyclization **13** → **7** (or more generally, **14** → **15**) that results in the formation of a new C–N bond at an unactivated olefinic carbon under mild conditions. In considering the nature of this reaction, we were attracted by the apparently analogous oxidative cyclizations[5] of the unsaturated hydroxylamine **16** to the nitroxide **17**[5a] and the *N*-chloroamine **18** to the bicyclic amine **19**.[5b] To examine this cyclization further, the unsaturated hydroxylamine **20** was synthesized by the route indicated in Scheme IV.

The synthesis of hydroxylamine **20** was initially complicated by the fact that the nitro olefin **22** was not reduced by a mixture of aluminum amalgam and H_2O in Et_2O or THF, conditions which reduce the seemingly analogous 3-nitro-3-methylpropane to **31** in high yield.[6] Consequently, the more vigorous reducing system, Zn and aqueous NH_4Cl, was employed[7] resulting in partial overreduction of the nitro olefin **22** to form a mixture of the hydroxylamine **20** and the amine **23**. The synthesis was further complicated by the instability of **20**; when mixtures containing this hydroxylamine **20** were either heated or allowed to stand, conversion to the cyclic hydroxylamine **24a** occurred and exposure of mixtures containing **20** to air resulted in rapid oxidation either to the cyclized products **24a** or **27** or to a

Scheme III



Scheme IV

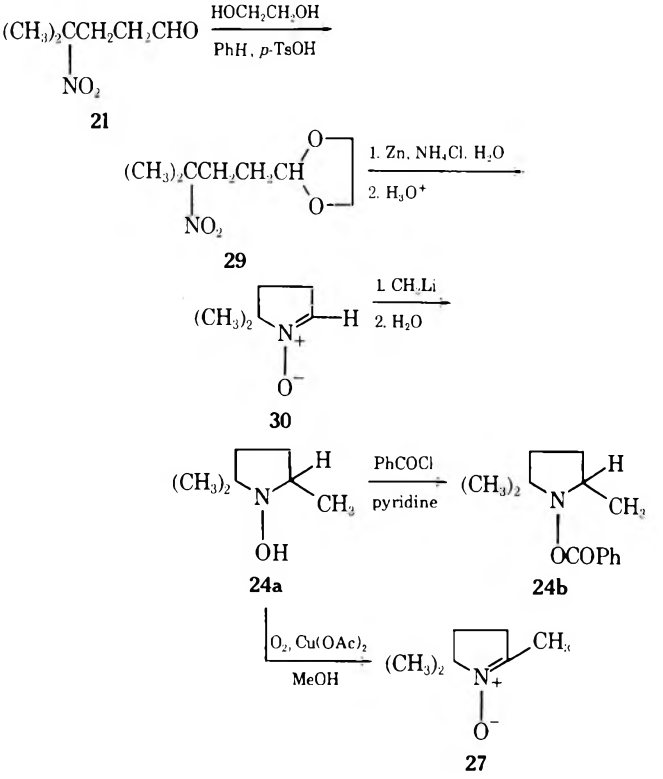


volatile blue material believed to be the nitroso compound **36**. These experimental difficulties were circumvented by acylating the mixture of the hydroxylamine **20** and the amine **23** to form mixtures of either the acetyl derivatives **25a** and **26** or the benzamide **25b** and the dibenzoyl derivative **28**. Each of these mixtures was separable by chromatography and the *N,O*-dibenzoyl derivative **28** was sufficiently stable to permit purification and complete characterization. Although the thermal instability of the liquid *O*-acetate **26** prevented us from obtaining it in analytically pure form, it was obtained in sufficient purity by chromatography to permit its use in a base-catalyzed methanolysis to generate solutions of the hydroxylamine **20** uncontaminated with the amine **23**. Solutions of this hydroxylamine **20**, obtained either from the nitro compound **22** or from the *O*-acetate **26**, underwent cyclization to the cyclic hydroxylamine **24a** (characterized as the benzoate **24b**) when either heated on a steam bath or allowed to stand overnight. Exposure of this cyclic hydroxylamine **24a** to O_2 (air), especially in the presence of a catalytic amount of a Cu(II) salt, resulted in oxidation to form the nitrone **27**.

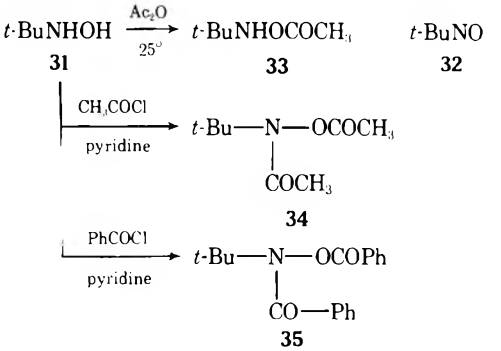
Authentic samples of the cyclic hydroxylamine **24a**, the benzoate **24b**, and the nitrone **27** were obtained from the nitrone **30** as indicated in Scheme V. Deliberate exposure of solution of the hydroxylamine **20** to O_2 resulted in the generation of a volatile, blue-colored material (presumable the nitroso compound **36**) and resulted in diminished yields of the cyclized products **24** and **27**. The best yield of benzoylated cyclized product **24b** (20% based on the *O*-acetate **26**)[8] was obtained when the most precautions were taken to minimize the concentration of O_2 present during the cyclization.

To examine the oxidation of *N*-alkyl hydroxylamines electrochemically, we studied the behavior of hydroxylamine derivatives **20**, **24a**, **26**, and also, as model compounds, hydroxylamine derivatives **31** and **33** (Scheme VI). It should be noted in passing that O-acylated *N*-alkyl hydroxylamines such as **26** and **33**, whose regioselective preparation has sometimes presented difficulty,[9] were readily prepared by reaction of the *N*-alkyl hydroxylamines **20** and **31** with Ac_2O *in the absence of pyridine*. By contrast, reaction of these hydroxylamines with either PhCOCl or CH_3COCl in the presence of pyridine yielded the N,O-diacylated derivatives **28**, **34**, and **35**. Neither the *O*-acetates **26** and **33** in MeOH solution nor the hydroxylamine **31** in DMF or in neutral (pH 7) aqueous solution exhibited a polarographic oxidation wave at a potential less positive than +0.2 V vs. SCE. As aqueous or methanolic solutions of **31** were made more basic, the oxidative wave shifted to progressively more negative potentials (corresponding to increasing ease of oxidation) with $E_{1/2}$ values of −0.20 V vs. SCE and −0.51 V vs. SCE being obtained for aqueous solutions of **31** at pH 10.0 and ca. 13, respectively.[10] This observation, taken with the estimated[9b] pK_a values 6 and 12–13 for the transformations $RN^+H_2OH - H^+ \rightarrow RNHOH - H^+ \rightarrow RNHO^-$, suggest that the hydroxylamine anion, $RNHO^-$, is probably the species responsible for the very

Scheme V



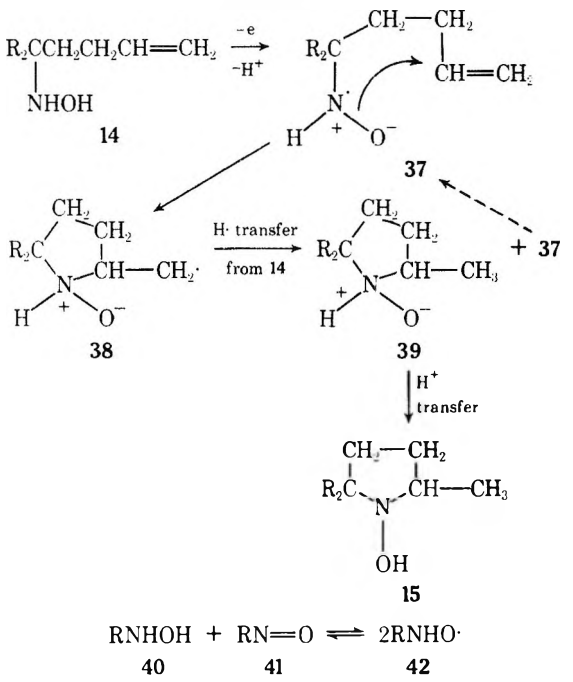
Scheme VI



ready air oxidation of RNHOH compounds in neutral and alkaline solution. In alkaline MeOH solution the hydroxylamines **31** ($E_{1/2}$ = −0.39 V vs. SCE), **20** ($E_{1/2}$ = −0.42 V vs. SCE, prepared from **26**), and **24a** ($E_{1/2}$ = −0.47 V vs. SCE) are all oxidized with about equal ease.

Consequently, our data suggest that the ring closure reaction being studied proceeds from the acyclic hydroxylamine **14** (or **20**) to the cyclic hydroxylamine **15** (or **24a**) and that subsequent formation of a nitrone such as **27** (or a nitroxide such as **17**[5a] where nitrone formation is not possible) is the result of oxidation of the intermediate cyclic hydroxylamine (e.g., **15**). Since the transformation **14** → **15** involves no net change in oxidation level and yet appears to be promoted by traces of oxidizing agents, we believe that the most reasonable interpretation involves a radical chain mechanism such as that illustrated in Scheme VII.[11c] In

Scheme VII



$$\underset{40}{\text{RNHOH}} + \underset{41}{\text{RN=O}} \rightleftharpoons \underset{42}{2\text{RNHO}\cdot}$$

this scheme only a catalytic amount of the intermediate nitroxide **37** is required to propagate the reaction chain and the subsequently formed carbon radical **38** (whose formation is analogous to the cyclization of a 5-hexenyl radical and to cyclization of the N radical derived from **18**) should be readily reduced by the hydroxylamine **15** present. Although the generation of the nitroxide **37** is formulated as a direct oxidation, it is also possible that the nitroxide arises by initial oxidation of a small amount of the starting hydroxylamine **40** to a nitroso compound **41** followed by the known[11a,b] interaction of **40** and **41** to produce a nitroxide **42**. This latter equilibration involving a nitroso compound is consistent with our observations that a faint blue color (attributable to **36**) was always observed when we generated a solution of the hydroxylamine **20** in the absence of a reducing agent.

We hope to define the scope and limitations of this cyclization reaction in synthesis from experiments now in progress. One preliminary experiment (see Experimental Section) with a solution of the hydroxylamine **31** in cyclohexene suggested that intermolecular analogues of the reaction **14** → **15** are not favorable.

Experimental Section[12]

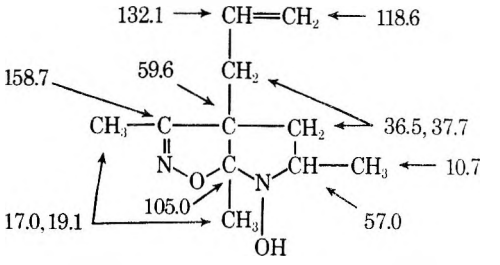
Reaction of the Diketone 5a with $HONH_2$. The diallyl diketone **5a**, obtained by the alkylation of 2,4-pentanedione,[13] exhibited the following NMR peaks (CCl_4): δ 4.8–5.9 (6 H, m, vinyl CH), 2.62 (4 H, d, J = 6 Hz, allylic CH_2), and 2.03 (6 H, s, CH_3CO). A solution of 60.0 g (0.33 mol) of the diketone **5a**, 23.2 g (0.33 mol) of $HONH_2$·HCl, and 27.9 g (0.33 mol) of NaOAc in 175 g of H_2O and 205 g of dioxane was refluxed for 6.5 h and then concentrated under reduced pressure. The residue was extracted with Et_2O and the Et_2O solution was dried and concentrated to leave 67.1 g of residual yellow liquid containing (GLC, silicone SE-30 on Haloport F) the diketone **5a** (retention time 3.4 min, ca. 2%), an unknown component (4.9 min, ca. 12%), and the isoxazoline **6a** (7.3 min, ca. 86%). A 34-g fraction of the crude product was distilled to separate 11.8 g of forerun [bp 84 °C (1.5 mm)–100 °C (0.5 mm)], and 17.2 g of the pure (GLC) isoxazoline **6a**: bp 100 °C (0.5 mm); ir (CCl_4) 3590, 3420 (broad, free and associated OH), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.8–6.2 (6 H, m, vinyl CH), 4.22 (1 H, s, OH), 1.9–2.9 (4 H, m, allylic CH_2), 1.83 (3 H, s, CH_3), and 1.47 (3 H, s, CH_3).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.37; H, 8.66; N, 7.15.

After a solution of 485 mg (2.69 mmol) of the diketone **5a**, 1.87 g (26.9 mmol) of $HONH_2$·HCl, and 220 mg (26.9 mmol) of NaOAc in 15 ml of H_2O and 15 ml of dioxane had been refluxed for 6 h, the reaction solution was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried, and concentrated to leave 539 mg of colorless liquid that was chromatographed on silica gel with Et_2O–hexane mixtures as eluents. After separation of 8 mg of an early fraction containing an uncharacterized solid (mp 192–198 °C), the subsequent fractions contained 441 mg (84%) of the liquid isoxazoline **6a** followed by 43 mg of the bicyclic hydroxylamine **7a**. The latter fraction was crystallized from hexane–Et_2O to separate 40 mg (7.1%) of one isomer of the bicyclic hydroxylamine **7a** as white prisms, mp 82–84 °C. When an analogous experiment was performed using 507 mg (2.59 mmol) of the isoxazoline with 1.80 g (25.9 mmol) of $HONH_2$·HCl and 2.13 g (25.9 mmol) of NaOAc, the bicyclic material **7a** isolated after chromatography and crystallization amounted to 40 mg (7.4%), mp 81.5–83.5 °C. Recrystallization raised the melting point of the bicyclic hydroxylamine **7a** to 88–89 °C: ir (CCl_4) 3580, 3420 (free and associated OH), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.9–6.0 (3 H, m, vinyl CH), 2.5–3.0 (1 H, m, NC<), 2.42 (2 H, d, J = 6.5 Hz, further partially resolved splitting apparent, allylic CH_2), 1.86 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 1.20 (3 H, d, J = 6 Hz, CH_3), and 1.1–2.0 (2 H, m, CH_2).

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.88; H, 8.91; N, 13.24.

The natural abundance ^{13}C NMR spectrum of hydroxylamine **7a**, measured in $CDCl_3$ solution with added Me_4Si, is summarized in the following structure. The chemical shift assignments, indicated in parts per million, are consistent with the spectrum measured with off-resonance decoupling.



Reaction of the hydroxylamine **7a** with excess PhCOCl in pyridine yielded a benzoate **8a**: mp 87–88 °C (mixture with **7a**, mp 66–82 °C); ir (CCl_4) 1755 cm^{-1} (ester C=O) with no absorption in the 3-μ region attributable to NH or OH groups; uv maxima (95% EtOH) 225 nm (ε 12500) and 271 (966); NMR (CCl_4) δ 8.0–8.3 (2 H, m, aryl CH), 7.3–7.7 (3 H, m, aryl CH), 5.0–6.2 (3 H, m, vinyl CH), 3.0–3.6 (1 H, m, NCH<), 2.48 (2 H, d, J = 6.5 Hz, allylic CH_2, further partially resolved splitting apparent), 1.85 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.3–2.1 (2 H, m, CH_2), and 1.13 (3 H, d, J = 6 Hz, CH_3).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.89, H, 6.99; N, 8.90.

Reaction of the Diketone 5b with $HONH_2$. The reaction of 3-methyl-2,4-pentanedione with allyl bromide and K_2CO_3 in acetone followed by fractional distillation afforded the diketone **5b** as a colorless liquid: bp 66–75 °C (5.7 mm), $n^{25}D$ 1.4504 [lit.[14] bp 85–89 °C (10 mm), $n^{25}D$ 1.4550]; ir (CCl_4) 1720, 1700 (C=O), and 1640 cm^{-1} (C=C); NMR (CCl_4) δ 4.8–5.9 (3 H, m, vinyl CH), 2.56 (2 H, d, J = 6.5 Hz, allylic CH_2), 2.3 (6, H, s, CH_3CO), and 1.27 (3 H, s,

CH_3). A solution of 17.79 g (115 mmol) of the diketone **5b**, 8.35 g (120 mmol) of $HONH_2$·HCl, and 9.84 g (120 mmol) of NaOAc in 100 ml of H_2O and 100 ml of dioxane was refluxed for 5 h and then concentrated under reduced pressure. The residue was partitioned between H_2O and CH_2Cl_2 and the organic layer was washed with H_2O, dried, and concentrated. Distillation of the residual liquid (17.32 g) separated 13.95 g (72%) of the crude isoxazoline **6b** as a colorless liquid, bp 87–89 °C (0.68 mm), that contained (TLC, silica gel coating) the stereoisomeric isoxazolines and a second more rapidly eluted component. Chromatography on silica gel with 40% Et_2O in hexane separated in the later fractions a mixture of the stereoisomeric isoxazolines **6b** as a colorless liquid: $n^{25}D$ 1.4831; ir (CCl_4) 3600, 3420 (broad, free and associated OH), and 1640 cm^{-1} (C=C); uv (95% EtOH) end absorption with ϵ 2860 at 210 nm; NMR (CCl_4) δ 4.8–6.3 (4 H, m, vinyl CH and OH, 1 H exchanged with D_2O), 2.0–3.0 (2 H, m, allylic CH_2), 1.87 (3 H, s, CH_3), 1.46 and 1.43 (two singlets, total 3 H, CH_3 of epimers), 1.12 (s, 39% of 3 H, CH_3 of one epimer), and 0.97 (s, 61% of 3 H, CH_3 of one epimer); mass spectrum *m/e* (rel intensity) 169 (11, M^+), 152 (42), 127 (33), 112 (60), 110 (59), 108 (69), 97 (76), 94 (37), 82 (56), 69 (58), 68 (94), 67 (100), 55 (30), 53 (49), 43 (69), 42 (45), 41 (39), and 39 (33).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.86; H, 8.97; N, 8.32.

To establish the stability of the isoxazoline **6b** to boiling H_2O, a solution of 111 mg of **6b** in 3 ml of H_2O was refluxed for 3 h and then cooled and extracted with $CHCl_3$. The extract was dried and concentrated to leave 109 mg of the unchanged isoxazoline **6b** that was identified by TLC analysis and comparison of ir spectra. A solution of 2.087 g (12.4 mmol) of the isoxazoline **6b**, 8.59 g (124 mmol) of $HONH_2$·HCl, and 10.12 g (124 mmol) of NaOAc in 45 ml of H_2O was refluxed for 2.5 h and then cooled, treated with $NaHCO_3$, and extracted with CH_2Cl_2. The organic extract was washed with H_2O, dried, and concentrated to leave 1.125 g of colorless liquid. Fractional crystallization from a PhH–hexane mixture separated 669 mg of isomer A of the hydroxylamine **7b** as white prisms, mp 85–92 °C, and 45 mg of isomer B of the hydroxylamine **7b** as white prisms, mp 147–156 °C. The mother liquor from these crystallizations was chromatographed on silica gel. The early fractions (eluent, 40% Et_2O in hexane) contained 28 mg of the crude solid dioxime **9**. Recrystallization (Et_2O–hexane) afforded the pure dioxime **9**, mp 167.5–169°, whose comparison with an authentic sample is described subsequently: ir ($CHCl_3$) 3580 and 3290 cm^{-1} (broad, free and associated OH); NMR (CD_3COCD_3) δ 9.67 and 2.91 (2 H, s, OH, exchanged with D_2O), 1.67 (6 H, s, CH_3), 1.20 (3 H, s, CH_3), and 0.8–1.9 (7 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 169 (18), 128 (100), 112 (34), 100 (21), 55 (32), 43 (37), 42 (47), and 41 (31).

Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.17; H, 9.82; N, 15.05.

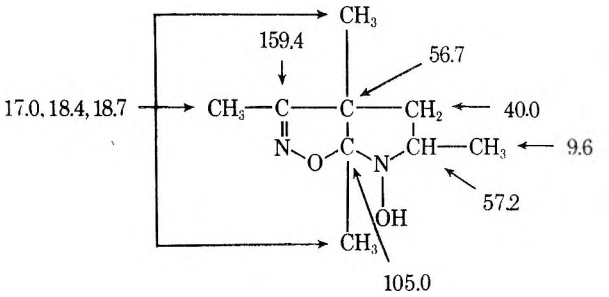
The next chromatographic fractions (eluent 70% Et_2O in hexane) contained 37 mg of isomer B of the hydroxylamine **7b**, mp 148–157 °C (total yield 82 mg or 3.6%). Recrystallization (Et_2O–hexane) separated the pure isomer B of the hydroxylamine **7b** as white prisms: mp 157–158.5 °C; ir ($CHCl_3$) 3570, 3350 (broad, free and associated OH), and 1620 cm^{-1} (C=N); uv (95% EtOH) end absorption with ϵ 2570 at 210 nm; NMR ($CDCl_3$) δ 6.25 (1 H, s, OH, exchanged with D_2O), 2.6–3.3 (1 H, m, NCH<), 1.88 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 1.21 (3 H, d, J = 6 Hz, CH_3), 1.18 (3 H, s, CH_3), and 1.2–1.8 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 184 (44 M^+), 128 (16), 127 (100), 126 (13), 112 (33), and 43 (13).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.79; H, 8.82; N, 15.33.

The final fractions from the chromatography contained 143 mg of isomer A of the hydroxylamine **7b**, mp 91–92 °C (total yield 812 mg or 36%). Recrystallization (PhH–hexane) afforded the pure isomer A of the hydroxylamine **7b** as white prisms: mp 91.5–92.5 °C; ir ($CHCl_3$) 3580, 3430 (OH), and 1630 cm^{-1} (C=N); uv (95% EtOH) end absorption with ϵ 3330 at 210 nm; NMR ($CDCl_3$) δ 4.7 (broad, 1 H, OH, exchanged with D_2O), 2.4–3.0 (1 H, m, NCH<), 1.85 (3, H, s, CH_3), 1.46 (3 H, s, CH_3), 1.20 (3 H, CH_3), 1.20 (3 H, d, J = 6 Hz, CH_3), and 1.2–2.1 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 184 (23, M^+), 127 (100), 112 (58), 110 (28), and 43 (14).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.82; H, 8.77; N, 15.10.

The natural abundance ^{13}C NMR spectrum of hydroxylamine **7b**, measured in $CDCl_3$ solution with added Me_4Si, is summarized in the following structure. The chemical shift assignments, indicated in parts per million, are consistent with the spectrum measured with off-resonance decoupling.



To a cold (0 °C) solution of 818 mg (4.45 mmol) of the hydroxylamine **7b**, isomer A, in 3 ml of anhydrous pyridine was added 1.0 ml of freshly distilled PhCOCl. The mixture, from which a white solid separated, was stirred for 30 min at 25 °C and then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried, and concentrated. The residual yellow liquid (1.724 g) was chromatographed on silica gel. The early fractions (473 mg, eluent 20% Et_2O in hexane) contained benzoic acid and the later fractions (1.262 g, eluent 50% Et_2O in hexane) contained the benzoate **8b** as a pale yellow liquid. Short-path distillation (150–152 °C at 0.03 mm) separated 981 mg (77%) of the benzoate **8b** as a viscous liquid: ir (CCl_4) 1755 cm^{-1} (ester C=O) with no absorption in the 3-μ region attributable to OH or NH groups; uv max (95% EtOH) 229 nm (ϵ 14 300), 278 (1050), and 280 (824); NMR (CCl_4) δ 7.8–8.3 (2, H, m, aryl CH), 7.2–7.7 (3 H, m, aryl CH), 2.9–3.6 (1 (1 H, m, NC<), 1.82 (3 H, s, CH_3), 1.34 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 1.12 (3 H, d, J = 6 Hz, CH_3), and 1.4–2.2 (2 H, m, CH_2); mass spectrum *m/e* (rel intensity) 288 (3, M^+), 125 (20), 122 (47), 111 (27), 105 (100), 96 (27), 77 (42), and 43 (20).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.41; H, 7.00; N, 9.65.

Reaction of 3-Methyl-3-propyl-2,4-pentanedione with $HONH_2$. A solution of 3.557 g (23.1 mmol) of the diketone **5b** in 20 ml of EtOAc was hydrogenated at 1 atm and 25 °C over 745 mg of a 5% Pt on carbon catalyst. After 4 h when 670 ml (1.3 equiv) of H_2 had been absorbed, the reaction was stopped and the reaction mixture was filtered and concentrated. A cold (0 °C) solution of the residual liquid in 35 ml of acetone was treated with excess aqueous 8 N H_2CrO_4. After this mixture had been stirred at 0 °C for 10 min, isopropyl alcohol was added to destroy the excess oxidant, and the solution was concentrated and partitioned between CH_2Cl_2 and dilute aqueous HCl. The organic layer was washed with H_2O, dried, concentrated, and distilled to separate 3.084 g (83%) of 3-methyl-3-propyl-2,4-pentanedione as a colorless liquid: bp 68–73 °C (4.7 mm); $n^{25}D$ 1.4360–1.4369; ir (CCl_4) 1720 and 1695 cm^{-1} (C=O); uv max (95% EtOH) 291 nm (ϵ 137); NMR (CCl_4) δ 2.02 (6 H, s, CH_3CO), 1.26 (3 H, s, CH_3), and 0.8–2.0 (7 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 104 (97), 85 (100), 57 (21), 43 (68), and 41 (34).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.36; H, 10.38.

A solution of 830 mg (5.32 mmol) of 3-methyl-3-propyl-2,4-pentanedione, 1.11 g (15.9 mmol) of $HONH_2$·HCl, and 1.31 g (15.9 mmol) of NaOAc in 20 ml of H_2O was refluxed for 3 h and the resulting suspension was cooled and extracted with EtOAc. The organic solution was washed with H_2O, dried, and concentrated to leave 838 mg of semisolid residue. Recrystallization from EtOAc–hexane separated 313 mg (32%) of the dioxime **9** as white needles, mp 165.5–167 °C. The product was identified with the previously described material by a mixture melting point determination and by comparison of ir spectra.

Preparation of the Ketone 10 and Its Oxime 11. To a cold (5–10 °C) solution of the enolate, obtained by reaction of 332 mmol of MeLi (halide-free, Foote Mineral Co.) in 350 ml of DME with 24.17 g (157 mmol) of 1-acetoxy-2-methylcyclohexene,[15] was added, rapidly and with stirring, 40.2 g (332 mmol) of freshly distilled allyl bromide. The resulting solution was stirred for 3 min and then partitioned between hexane and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and fractionally distilled to separate 11.7 g (48%) of the ketone **10** as a colorless liquid, bp 92–100 °C (20 mm), $n^{25}D$ 1.4693 [lit.[16] bp 85–87 °C (12 mm)]. This product **10** exhibited a single GLC peak (silicone gum, SE-30, on Chromosorb P) at 7.5 min and did not contain any significant amount of 2-methylcyclohexanone (GLC retention time 3.5 min): ir (CCl_4) 1710 (C=O) and 1642 cm^{-1} (C=C); uv max (95% EtOH) 288 nm (ϵ 45); NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH), 2.0–2.5 (4 H, m, CH_2CO and allylic CH_2), 1.5–2.0 (6 H, m, aliphatic CH_2),

and 1.02 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 152 (M^+, 52), 137 (53), 109 (75), 95 (53), 93 (78), 83 (64), 81 (50), 68 (54), 67 (81), 55 (100), and 41 (68).

A solution of 1.271 g (8.37 mmol) of the ketone **10**, 1.81 g (26 mmol) of $HONH_2$·HCl, and 3.5 g (26 mmol) of NaOAc in 10 ml of H_2O and 10 ml of EtOH was refluxed for 6 h and then cooled and partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic solution was washed with aqueous NaCl, dried, and concentrated to leave 1.392 g of colorless liquid. Crystallization from H_2O–EtOH separated 1.069 g (77%) of the oxime **11** in fractions melting in the range 44–50 °C. Recrystallization afforded the pure oxime **11** as white plates: mp 48.5–50 °C; ir (CCl_4) 3240 (associated OH) and 1640 cm^{-1} (weak, C=C); uv (95% EtOH) end absorption with ϵ 2790 at 204 nm; NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH), 1.5–3.1 (10 H, m, aliphatic CH), and 1.10 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 167 (M^+, 20), 152 (32), 126 (100), 81 (32), 67 (25), 55 (26), and 41 (47).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found, C, 71.89; H, 10.06; N, 8.60.

Preparation of the Aldehyde 21.[17] To a cold (−14 °C) mixture of 320 g (2.57 mol) of 2-nitropropane (freshly distilled) and 18 ml of methanolic 40% $PhCH_2N^+Me_3OH^-$ was added, dropwise with stirring and cooling (−10 to −14 °C) during 2 h, a solution of 27.0 g (0.477 mol) of acrolein in 110 g (1.26 mol) of 2-nitropropane (freshly distilled). The resulting dark green solution was acidified to pH 5 by the dropwise addition of aqueous 3 M HCl and the resulting pale yellow solution was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure (20 mm) to remove the excess 2-nitropropane. Short-path distillation of the residual yellow liquid separated 31.0 g of crude product as a yellow liquid, bp 85–90° (3 mm). The crude product was redistilled through a 17-cm Vigreux column, keeping the still pot temperature in the range 78–90 °C, to separate 29.9 g (41%) of the nitro aldehyde **21** as a colorless liquid: bp 61–64 °C (0.12 mm), $n^{25}D$ 1.4460 [lit.[18] bp 88.3–89.5 °C (3 mm), $n^{19}D$ 1.4469]; ir (CCl_4) 2721, 2825 (aldehyde CH), 1728 (C=O), 1538 and 1349 cm^{-1} (NO_2); NMR (CCl_4) δ 9.80 (1 H, s, aldehyde CH), 2.0–2.7 (4 H, m, CH_2), and 1.57 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 99 (10), 81 (100), 70 (21), 69 (38), 57 (21), 56 (31), 55 (76), 53 (21), 43 (72), 41 (79), and 39 (39). The product exhibited one major GLC peak (silicone SE-30 on Chromosorb P) at 4.8 min with a minor unidentified impurity at 3.7 min.

Preparation of the Nitro Olefin 22.[17] A solution of $Ph_3P{=}CH_2$, prepared from 64.0 g (0.18 mol) of $Ph_3P^+CH_3Br^-$ in 500 ml of THF and 0.17 mol of MeLi in 98 ml of Et_2O was treated with a solution of 20.0 g (0.138 mol) of the aldehyde **21** in 50 ml of THF. The resulting mixture, from which a white precipitate separated, was refluxed for 24 h and then cooled. After the reaction mixture had been washed with H_2O, the aqueous phase was extracted with Et_2O and the combined organic layers were dried and concentrated under reduced pressure. The residual brown liquid was triturated with pentane to separate the insoluble Ph_3PO and the resulting pentane solution was concentrated to leave 17.0 g of crude product as a yellow liquid. Distillation separated 11.5 g (58%) of the pure nitro olefin **22** as a colorless liquid: bp 45–47 °C (2 mm); $n^{25}D$ 1.4392; ir (CCl_4) 1640 (C=C), 1530, 1345 (NO_2), 992, and 918 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.2 (3 H, m, CH=CH_2), 1.8–2.4 (4 H, m, CH_2), and 1.57 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 97 (32), 81 (51), 55 (65), 43 (41), 41 (55), 40 (42), and 39 (23). The product exhibits one major GLC peak (silicone SE-30 on Chromosorb P) at 4.9 min.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.74; H, 9.16; N, 9.74.

Reduction of the Nitro Olefin 22. To a cold (10 °C) mixture of 5.60 g (39 mmol) of the nitro olefin **22**, 5 ml of H_2O, 10 ml of Et_2O, and 4.2 g (78 mmol) of NH_4Cl was added portionwise and with vigorous stirring during 20 min, 20.0 g (306 mg-atoms) of Zn dust. Throughout this reduction, the reaction mixture was kept under an N_2 atmosphere and was cooled with an ice–water bath. During the addition of Zn, the reaction mixture assumed a light blue color and the temperature rose to 15°. After the mixture had been stirred at 15 °C for 20 min, it was treated successively with 4 ml of H_2O, 2.00 g (37.4 mmol) of NH_4Cl, and 5 ml of Et_2O. Then an additional 5.0 g (76.4 mg-atoms) of Zn dust was added, portionwise with cooling and stirring during 10 min. After addition of this second portion of Zn dust, the pale blue color disappeared and the resulting colorless reaction mixture was stirred at 15–20 °C for 20 min. The reaction mixture was filtered and the residue was washed repeatedly with Et_2O. The combined ethereal filtrates were dried and added to 20 ml of Ac_2O. After the resulting solution had been allowed to stand for 20 min, it was stirred with 50 ml of saturated aqueous $NaHCO_3$ for 20 min and then the Et_2O layer was separated, washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated. Fractional crystallization of the residual yellow liquid (4.25 g) from pentane at dry ice temperature separated 1.5 g (15%) of the acetamide **25a** as colorless needles: mp 53–55 °C; ir ($CHCl_3$) 3415 (NH), 1670 (amide C=O), 1640 (C=C), and 910 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 4.7–6.2 (4 H, m, NH and CH=CH_2), 1.6–2.3 (7 H, m, CH_2 and a CH_3CO singlet at 1.92), and 1.30 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 155 (M^+, 4), 100 (47), 98 (22), 81 (21), 60 (37), 58 (100), and 43 (20).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.84; H, 11.05; N, 9.07.

The mother liquors from this crystallization were concentrated and the residual liquid (2.5 g) was chromatographed on 80 g of silica gel with Et_2O–pentane mixtures as the eluent. After separation of 58 mg of early fractions of unidentified liquid [1:99 to 3:97 (v/v) Et_2O–pentane eluent], subsequent fractions, eluted with a 1:9 (v/v) Et_2O–pentane mixture, contained 1.98 g (30%) of the *O*-acetyl hydroxylamine **26** as a colorless liquid: $n^{25}D$ 1.4410; ir (CCl_4) 3220 (NH), 1740 (ester C=O), 1640 (C=C), and 915 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 7.42 (1 H, broad NH), 4.8–6.2 (3 H, m, CH=CH_2), 1.8–2.4 (5 H, m, allylic CH_2 with a CH_3CO singlet at 2.04), 1.2–1.8 (2 H, m, CH_2), and 1.07 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 116 (22), 96 (23), 74 (49), 56 (96), 55 (100), and 43 (57). Our efforts to obtain an analytically pure sample of the *O*-actate **26** from these chromatographic fractions were thwarted by the partial thermal decomposition of this material during each attempt to distill it.

In another experiment 2.00 g (13.3 mmol) of the nitro olefin **22** was reduced with 1.50 g (28 mmol) of NH_4Cl, 10 ml of Et_2O, 4 ml of H_2O, and 11.0 g (167 mg-atoms) of Zn dust. An Et_2O solution of the product (141 ml) was divided into two aliquots (41 and 100 ml).

The 41-ml aliquot was concentrated under reduced pressure to leave 353 mg of yellow liquid that contained (NMR analysis) a mixture of the hydroxylamine **20** (ca. 75%) and the amine **23** (ca. 25%): NMR (CCl_4) δ 4.8–6.2 (ca. 5 H, m, CH=CH_2, NH, and OH), 1.3–2.4 (ca. 4 H, m, CH_2), and two singlets (total ca. 6 H) at 1.12 (CH_3 of amine **23**) and 1.05 (CH_3 of hydroxylamine **20**). After standing overnight under an N_2 atmosphere, the NMR absorption of the sample was very different with much less intense absorption attributable to the vinyl group and replacement of the singlet at δ 1.05 (CH_3 of **20**) with a series of peaks in the region δ 1.0–1.3 attributable to the CH_3 signals of the cyclic hydroxylamine **24a**. Because of the instability of the unsaturated hydroxylamine **20**, we were unable to separate the initially formed mixture of bases **20** and **23**. The sample (containing **23** and **24a**) was added to a cold (5 °C) solution of 2 ml of PhCOCl in 4 ml of pyridine. After the resulting solution had been allowed to stand at 25 °C for 1 h, it was partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried, concentrated, and chromatographed on silica gel with PhH as an eluent. After removal of the initial fractions containing $(PhCO)_2O$, subsequent fractions contained 459 mg of the crude benzoate **24b** which was dissolved in Et_2O, washed with aqueous $NaHCO_3$,[19] dried, and concentrated to leave 305 mg (34%) of the benzoate **24b** (ir and NMR analysis) as a yellow liquid. Further purification of this sample by preparative TLC [silica gel coating with a 5:1 (v/v) hexane–Et_2O eluent] and short-path distillation (at 0.3 mm with a Kragen tube) afforded a sample of the pure benzoate **24b** as a colorless liquid, $n^{25}D$ 1.5142, that was identified with a subsequently described authentic sample by comparison of ir, NMR, uv, and mass spectra.

The 100-ml aliquot of ethereal solution (containing **20** and **23**) from the previously described reduction was mixed with 15 ml of acetic anhydride and allowed to stand at 25 °C for 2 h, and subjected to the previously described isolation procedure to give 1.25 g of product as a pale yellow liquid containing [TLC, silica gel coating with a 1:1 (v/v) PhH–Et_2O eluent] a mixture of the acetate **26** (R_f 0.64) and the acetamide **25a** (R_f 0.30). A 520-mg aliquot of this mixture was chromatographed on silica gel to separate 220 mg (31%) of the acetate **26** as a yellow liquid, $n^{25}D$ 1.4420. The remaining aliquot containing a mixture of **25a** and **26** was stirred at 25° with 10 ml of aqueous 10% NaOH for 12 h. The resulting mixture was neutralized with aqueous HCl and extracted with Et_2O. After the ethereal extract had been dried and concentrated the residual liquid (360 mg) was crystallized twice from hexane at low tempera-

tures to separate 75 mg (9%) of the amide **25a** as white needles, mp 52–53 °C.

In another experiment, 1.50 g (10.5 mmol) of the nitro olefin **22** was reduced as described previously with a mixture of Zn, NH_4Cl, H_2O, and Et_2O and the crude product (TLC analysis, a mixture of unchanged **22**, amine **23**, and hydroxylamine **20**) was obtained as 140 ml of an Et_2O solution. An 80-ml aliquot was concentrated under reduced pressure and the residual liquid (0.32 g) was added to a solution of 3 ml of PhCOCl in 6 ml of pyridine. After this solution had been allowed to stand for 1 h at 25 ° C, it was partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal phase was dried, concentrated, and chromatographed on silica gel with a 1:1 (v/v) hexane–PhH eluent. After separation of the early fractions containing $(PhCO)_2O$, subsequent fractions afforded 392 mg of a crude liquid product ($PhCO_2H$, **25b**, and **28**). An Et_2O solution of this material was washed with aqueous $NaHCO_3$, dried, concentrated, and fractionally crystallized from pentane at low temperatures to separate 78 mg (6%) of the benzamide **25b**, mp 88–90 °C. Recrystallization afforded the pure benzamide **25b** as colorless needles: mp 90–91°; ir (CCl_4) 3420 (NH), 1670 (amide C=O), 1640 (C=C), and 910 cm^{-1} (CH=CH_2); uv max (95% EtOH) 222 nm (ϵ 11 000); NMR (CCl_4) δ 7.0–7.8 (5 H, m, aryl CH), 5.7–6.2 (4 H, m, NH and CH=CH_2), 1.7–2.2 (4 H, m, CH_2), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 217 (M^+, 2), 162 (20), 122 (25), 105 (100), and 77 (36).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 8.85; N, 6.51.

The mother liquor from crystallization of the amide **25b** was concentrated and the residual liquid (275 mg) was subjected to preparative TLC separation [silica gel coating with a 3:7 (v/v) Et_2O–pentane eluent]. The more rapidly moving component was separated as 119 mg of pale yellow liquid that crystallized from pentane at low temperatures to give 78 mg (4%) of the dibenzoyl derivative **28** as colorless needles: mp 62.5–63.5 °C; ir (CCl_4) 1768 (ester C=O), 1668 (broad, amide C=O), and 910 cm^{-1} (CH=CH_2); uv max (95% EtOH) 232 nm (ϵ 15 000); NMR (CCl_4) δ 7.0–7.9 (10 H, m, aryl CH), 4.8–6.0 (3 H, m, CH=CH_2), 1.7–2.7 (4 H, m, CH_2), and 1.48 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 242 (1), 200 (9), 162 (11), 122 (17), 105 (100), and 77 (28).

Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.66; H, 6.87; N, 4.17.

From an additional reduction of 2.0 g (14 mmol) of the nitro olefin **22** with Zn, NH_4Cl, H_2O, and Et_2O), the crude product contained (NMR analysis) a mixture of the hydroxylamine **20** (ca. 45%) and the amine **23** (ca. 55%). An aliquot (38% of the total) of this mixture was concentrated to leave 400 mg of crude product that was heated on a steam bath for 5 min after which NMR analysis indicated the crude product to be a mixture containing mainly the amine **23** and the cyclized hydroxylamine **24a**. This crude product was dissolved in 5 ml of MeOH containing 2 mg of $Cu(OAc)_2$ and air was passed through the solution for 5 min to oxidize the hydroxylamine **24a**. The resulting solution was concentrated and the residue was distilled in a short-path still to separate 55 mg (8% based on the starting nitro olefin **22**) of the nitrone **27** as a yellow liquid, $n^{25}D$ 1.4842. This product was identified with a subsequently described authentic sample of the nitrone **27** by comparison of ir, NMR, uv, and mass spectra.

Preparation of Authentic Samples of the Cyclic Hydroxylamine Derivatives 24 and the Nitrone 27. Following previously described procedures,[20] 8.00 g (55.2 mmol) of the nitro aldehyde **21** was converted to 8.00 g (77%) of the nitro acetal **29** as a colorless liquid: bp 98–99 °C (1 mm), $n^{25}D$ 1.4535 [lit.[20a] bp 105 °C (0.5 mm)]; ir (CCl_4) 1535 and 1345 cm^{-1} (NO_2); NMR (CCl_4) δ 4.78 (1 H, t, J = 4 Hz, acetal CH), 3.7–4.0 (4 H, m, CH_2O), 1.3–2.2 (10 H, m, CH_2 and a CH_3 singlet at 1.57). Subsequent reduction of 5.00 g (26.4 mmol) of the nitro acetal **29** with Zn dust and aqueous NH_4Cl[20b] followed by acidification and cyclization yielded 2.32 g (76%) of the nitrone **30** as a colorless liquid: bp 78 °C (1.4 mm), $n^{25}D$ 1.4940 [lit.[20b] bp 66–67 °C (0.6 mm)]; ir ($CHCl_3$) 1578 cm^{-1} (CH=N^+–O^-); uv max (95% EtOH) 234 nm (ϵ 8660) [lit.[20b] 234 nm (ϵ 7700)]; NMR ($CDCl_3$) δ 6.78 (1 H, t, J = 2.5 Hz, CH=N^+–O^-), 2.0–2.8 (4 H, m, CH_2), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 113 (M^+, 100), 81 (34), 67 (33), 57 (46), 56 (30), 55 (70), 43 (36), 41 (89), and 39 (61). To 5 ml of an Et_2O solution containing 8.5 mmol of MeLi was added a solution of 354 mg (3.13 mmol) of the nitrone **30** (dried by partial distillation of the solvent from a PhH solution) in 10 ml of Et_2O. The resulting solution was refluxed with stirring for 15 min and then hydrolyzed by addition of 0.5 ml of aqueous NH_4Cl. The Et_2O solution was separated, dried, and concentrated to leave 320 mg of the crude hydroxylamine **24a** as a yellow liquid: NMR (CCl_4) δ 2.7–3.3 (ca. 1 H, m, CHN), 0.9–2.1 [ca. 14 H, m, CH_2, OH, and CH_3 singlets at 1.17 and 1.00 as well as a CH_3 doublet (J = 6 Hz) at 1.17]. This crude product (320 mg) was dissolved in 6 ml of pyridine, cooled in ice, and treated with 2 ml of PhCOCl. After the resulting solution had been stirred for 15 min, it was partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O phase was dried and concentrated to leave 872 mg of residual brown liquid that was chromatographed on silica gel. After removal of early fractions, which were eluted with PhH and contained $(PhCO)_2O$ and $PhCO_2H$, subsequent fractions, eluted with PhH–Et_2O mixtures (20:1 v/v), were partitioned between Et_2O and aqueous $NaHCO_3$ and then dried and concentrated to leave 313 mg (43%) of the crude benzoate **24b** as a brown liquid. This material was further purified by preparative TLC (silica gel coating with a hexane–Et_2O eluent, 5:1 v/v) followed by short-path distillation under reduced pressure in a Kragen tube to separate the pure benzoate **24b** as a pale yellow liquid: $n^{25}D$ 1.5138; ir (CCl_4) 1750 cm^{-1} (ester C=O); uv max (95% EtOH) 228 nm (ϵ 12 000), 273 (1000), and 279 (820); NMR (CCl_4) δ 7.2–8.2 (5 H, m, aryl CH), 3.1–3.6 (1 H, m, CHN), 1.4–2.3 (4 H, m, CH_2), and three partially resolved CH_3 signals (9 H total) consisting of two singlets at 1.20 and 1.17 with a partially resolved doublet (J = ca. 6 Hz) at ca. 1.17; mass spectrum *m/e* (rel intensity) 122 (82), 111 (40), 105 (89), 96 (36), 83 (68), 77 (58), 70 (55), 55 (56), and 42 (100).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.93; H, 8.27; N, 5.97.

After a comparable reaction of 1.0 g (8.9 mmol) of the nitrone **30** with 14.1 mmol of MeLi in 13 ml of Et_2O, the crude hydroxylamine product **24a** (0.90 g) was dissolved in 5 ml of MeOH containing 1 mg of $Cu(OAc)_2$ and air was passed through the solution for 10 min. After the resulting mixture had been allowed to stand for 24 h, it was concentrated and the residual liquid was distilled under reduced pressure in a short-path still to separate 0.44 g (40%) of the nitrone **27** as a yellow liquid: $n^{25}D$ 1.4835; ir (CCl_4) 1600 cm^{-1} (>C=N^+–O^-); uv max (95% EtOH) 229 nm (ϵ 7300) [lit.[20c] 231 nm (ϵ 8400)]; NMR ($CDCl_3$) δ 2.4–2.9 (2 H, m, CH_2C=N), 1.8–2.2 (5 H, m, CH_2 and a broad CH_3 singlet at 2.02), and 1.40 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 127 (M^+, 77), 112 (36), 95 (24), 69 (23), 58 (37), 55 (46), 43 (85), 42 (39), 41 (100), and 39 (26).

Preparation of Acyl Derivatives of *t*-BuNHOH (31). Samples of *t*-BuNHOH (**31**) and the dimer of *t*-BuNO (**32**) were prepared by previously described procedures.[6] A solution of 1.00 g (11 mmol) of *t*-BuNHOH in 3.0 ml of Ac_2O was allowed to stand at 25° for 20 min and then the mixture was partitioned between Et_2O and aqueous $NaHCO_3$. After the Et_2O layer had been dried and concentrated, distillation of residual yellow oil (200 mg) under reduced pressure in a short-path still separated 157 mg (11%) of the acetate **33** as a colorless liquid: $n^{25}D$ 1.4100; ir (CCl_4) 3210 (NH) and 1735 cm^{-1} (ester C=O); NMR (CCl_4) δ 7.37 (1 H, broad, NH, exchanged with D_2O), 2.05 (3 H, s, CH_3CO), and 1.08 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 118 (1), 115 (4), 72 (15), 70 (16), 60 (25), 58 (100), 57 (73), 56 (42), 55 (31), 44 (38), 43 (62), 42 (45), 41 (60), and 39 (42).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.89; H, 10.01; N, 10.70.

A solution of 0.50 g (5.6 mmol) of *t*-BuNHOH in 6.0 ml of pyridine was treated with 3.0 ml of CH_3COCl and the resulting semisolid mixture was allowed to stand at 25 °C for 20 min. The reaction mixture was partitioned between Et_2O and aqueous $NaHCO_3$ and the Et_2O layer was dried and concentrated. The residual liquid (310 mg) was chromatographed on silica gel. After separation of early unidentified fractions (8 mg), the crude ester amide **34** was eluted with hexane–Et_2O (9:1 v/v) as 220 mg of pale yellow liquid. Distillation under reduced pressure in a short-path still separated 200 mg (21%) of the pure ester amide **34** as a colorless liquid: $n^{25}D$ 1.4350 [lit.[21] bp 102 °C (19 mm)]; ir (CCl_4) 1795 (ester C=O) and 1688 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.15 (3 H, s, CH_3COO), 1.85 (3 H, s, CH_3CON), and 1.37 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 173 (M^+, 1), 131 (24), 57 (57), 56 (28), and 43 (100).

A cold (5 °C) solution of 300 mg (3.4 mmol) of *t*-BuNHOH in 6.0 ml of pyridine was treated with 3.0 ml of PhCOCl and the resulting mixture was allowed to stand at 25 °C for 1 h. After the reaction mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the Et_2O layer was dried and concentrated to leave 1.8 g of liquid. Chromatography on silica gel with a PhH–hexane eluent (1:1 v/v) separated $(PhCO)_2O$ in early fractions followed by 1.07 g of liquid containing the ester amide **35**. Crystallization from pentane afforded 200 mg (20%) of the pure ester amide **35** as colorless

needles: mp 97–99 °C (lit.[21] mp 98–99 °C); ir (CCl_4) 1768 (ester C=O) and 1678 cm^{-1} (amide C=O); uv max (95% EtOH) 233 nm (ϵ 17 000); NMR (CCl_4) δ 7.1–7.9 (10 H, m, aryl CH) and 1.58 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 105 (100), 77 (31), 51 (11), and 41 (5).

To examine the possibility of an intermolecular addition of *t*-BuNHOH to an olefin, a solution of 1.0 g (11.2 mmol) of *t*-BuNHOH and 1 mg of the dimer of *t*-BuNO in 10 g (122 mmol) of freshly purified cyclohexene was heated to 60° under an N_2 atmosphere with stirring for 16 h and then concentrated under reduced pressure. The NMR spectrum (CCl_4) of the residual solid (0.50 g) exhibited only NMR peaks attributable to *t*-BuNHOH with no indication that *N*-*tert*-butyl-*N*-cyclohexylhydroxylamine had been formed.

Methanolysis of the *O*-Acetates 26 and 33 and Cyclization of the Hydroxylamine 23. A solution of 30 mg (0.22 mmol) of the *O*-acetate **33** in 150 μl of MeOH exhibited NMR singlets at δ 2.08 ($COCH_3$) and 1.19 (*t*-Bu). Upon dropwise addition of methanolic 1 M NaOH, 10 μl (0.01 mmol) was required to catalyze the complete conversion of the *O*-acetate **33** to $MeOCOCH_3$ (NMR singlet at δ 2.02) and the hydroxylamine **31** (NMR singlet at δ 1.10) at 25 °C. Similarly, when a solution of 30 mg (0.18 mmol) of the *O*-acetate **26** in 200 μl of MeOH at 25° (NMR singlets at δ 2.09 and 1.01) was treated with 30 μl (0.03 mmol) of methanolic 1 M NaOH, the solution contained CH_3OCOCH_3 (NMR singlet at δ 2.02) and the hydroxylamine **26** (NMR singlet at δ 1.05). When this solution of the hydroxylamine **26** was refluxed for 5 min, the NMR spectra of the solution exhibited a multiplet in the region δ 1.0–1.2 characteristic of the cyclic hydroxylamine **24a.**

This conversion was repeated on a larger scale by treating a solution of 445 mg (2.6 mmol) of the *O*-acetate **26** in 5 ml of MeOH with 200 mg (5.0 mmol) of NaOH. The solution, which immediately turned pale blue in color, was stirred under N_2 for 2 min, neutralized with CO_2, and filtered to remove the $NaHCO_3$ precipitate. The residue was washed with Et_2O and the combined organic solutions were concentrated under reduced pressure to leave 220 mg of the crude liquid hydroxylamine **20.** This crude product was heated on a steam bath for 2 min and then cooled and treated with 1.0 ml of PhCOCl and 2.0 ml of pyridine. The resulting mixture was stirred for 10 min at 25° and then partitioned between Et_2O and aqueous 3 M HCl. After the ethereal layer had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual crude product (912 mg) was chromatographed on silica gel with Et_2O–pentane mixtures as eluents. After separation of the early fractions [mixtures of $(PhCO)_2O$ and $PhCO_2H$], the fractions (350 mg of yellow liquid) eluted with 1:1 (v/v) Et_2O–pentane mixtures were partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was dried and concentrated and the residue (308 mg) was rechromatographed on silica gel to separate 180 mg (20% yield based on the acetate **26**) of the liquid benzoate **24b,** $n^{25}D$ 1.5130, that was identified with the previously described authentic sample by comparison of ir and NMR spectra.

Electrochemical Measurements. The polarographic and cyclic voltammetry measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three-electrode design. Descriptions of the cells, working electrodes (Pt sphere electrode for cyclic voltammetry and dropping Hg electrode for polarography), reference electrodes, reagent purification procedures, and procedures used to calculate $E_{1/2}$ values have been published previously.[22] The polarographic reduction of solutions of the nitroso compound **32** ($6.7–8.9 \times 10^{-3}$ M) in anhydrous DMF containing 0.5 M *n*-Bu_4NBF_4 gave $E_{1/2} = -1.48$ V vs. SCE (n = 0.8, i_d = 39–44 μA).[23] Reduction of the same solution by cyclic voltammetry (scan rate 500 mV/s) gave a cathodic peak at −1.86 V vs. SCE but no anodic peak was observed. When sufficient H_2O was added to make the solution 1.0 M in H_2O, the cathodic peak was shifted to −1.75 V vs. SCE and an anodic peak, attributable to an unidentified reaction product, was observed at −0.87 V vs. SCE. Attempts to examine the oxidation of *t*-BuNHOH by cyclic voltammetry in a 0.5 M solution of *n*-Bu_4NBF_4 in either anhydrous DMF or in DMF containing 1 M H_2O gave no oxidation peak within the range −1.3 to +0.5 V. Similarly, a solution of *t*-BuNHOH in an aqueous buffer (pH 7.0) exhibited no polarographic oxidation wave in the range −0.5 to +0.2 V vs. SCE. In more basic solution, the oxidation wave was shifted to more negative values.[24] In aqueous pH 10.0 buffer, the *t*-BuNHOH ($8.3–8.5 \times 10^{-3}$ M) solution exhibited an oxidation wave with $E_{1/2}$ −0.20 V vs. SCE (n = 0.9, i_d = 48–52 μA) and in a more alkaline aqueous solution (pH ~ 13, 1.5 M Na_2SO_3 and 0.14 M KOH),[25] *t*-BuNHOH ($6.7–7.6 \times 10^{-3}$ M) exhibited an $E_{1/2}$ value of −0.51 V vs. SCE (n = 1.5, i_d = 46–47 μA). A solution of the *O*-acetate **33** (0.009 M) in aqueous MeOH (15:85 v/v) containing 0.5 M *n*-Bu_4NBF_4 exhibited no polarographic oxidation wave in the range −0.5 to 0.0 V; when sufficient methanolic NaOH solution was added to saponify the *O*-acetate **33** and make the solution 0.05 M in NaOH, a polarographic oxidation wave attributable to **31** was observed with $E_{1/2}$ = −0.39 V vs. SCE (n = 1.0, i_d = 24 μA). Comparable behavior was observed for the *O*-acetate **26** ($2.7–12 \times 10^{-3}$ M) whose solution in aqueous MeOH containing 0.5 M *n*-Bu_4NBF_4 exhibited no polarographic oxidation wave in the range −0.5 to 0.0 V. After addition of methanolic NaOH to saponify the acetate **26** and make the solution 0.05 M in NaOH, this solution of the hydroxylamine **20** exhibited a polarographic oxidation wave at $E_{1/2}$ = −0.42 V vs. SCE (n = 1.1, i_d = 5–27 μA). The polarographic oxidation of this solution was reexamined at intervals after the solution had been stirred under N_2 and after the solution had been exposed to O_2 of the air. The i_d value decreased regularly as the solution was stirred but no new oxidation peak was observed. After exposure to O_2 of the air for 10 min, the oxidation wave attributable to hydroxylamines **20** and/or **24a** was no longer observed indicating that oxidation of **20** to the corresponding nitroso compound or **24a** to the nitrone **27** was complete. Polarographic oxidation of a solution of the cyclic hydroxylamine **24a** ($1.4–2.0 \times 10^{-2}$ M) in aqueous MeOH (15:85 v/v) containing 0.5 M *n*-Bu_4NBF_4 and 0.05 M NaOH gave $E_{1/2}$ = −0.47 V vs. SCE (n = 0.8, i_d = 19–24 μA). Since the $E_{1/2}$ values for oxidation of the hydroxylamine **20** before (−0.42 V) and after cyclization (to form **24a,** $E_{1/2}$ = −0.47 V) are very similar, our failure to observe two resolved oxidation waves during the change **20** → **24a** → **27** is understandable.

Registry No.—**5a,** 3508-79-0; **5b,** 53315-95-0; **6a,** 57620-40-3; **6b,** 57620-41-4; **7a,** 57620-42-5; **7b,** 57620-43-6; **8a,** 57620-44-7; **8b,** 57620-45-8; **9,** 57620-46-9; **10,** 16178-87-3; **11,** 57620-47-0; **20,** 57620-48-1; **21,** 57620-49-2; **22,** 57620-50-5; **23,** 819-45-4; **24a,** 57620-51-6; **24b,** 57620-52-7; **25a,** 57620-53-8; **25b,** 835-85-8; **26,** 57620-54-9; **27,** 4567-18-4; **28,** 57620-55-0; **29,** 57620-56-1; **30,** 3317-61-1; **31,** 16649-50-6; **33,** 51338-99-9; **34,** 53242-00-5; **35,** 51339-08-3; $HONH_2$·HCl, 5470-11-1; PhCOCl, 98-88-4; 3-methyl-2,4-pentanedione, 815-57-6; allyl bromide, 106-95-6; 3-methyl-3-propyl-2,4-pentanedione, 57620-57-2; methyllithium, 917-54-4; 1-acetoxy-2-methylcyclohexene, 1196-73-2; 2-nitropropane, 79-46-9; acrolein, 107-02-8; methylenetriphenylphosphorane, 3487-44-3; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5.

References and Notes

(1) This research has been supported in part by Public Health Service Grant 9-RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institution Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.
(2) (a) Georgia Institute of Technology; (b) Union Carbide Corp.
(3) D. T. Manning and H. A. Coleman, *J. Org. Chem.*, **34,** 3248 (1969).
(4) This experiment was performed in our laboratories by Dr. R. A. Auerbach.
(5) (a) W. B. Motherwell and J. S. Roberts, *Chem. Commun.*, **No. 6,** 328, 329 (1972). We are indebted to Dr. James S. Roberts, who supplied additional experimental details concerning the preparation and cyclization of hydroxylamine **16.** (b) J. M. Surzur and L. Stella, *Tetrahedron Lett.*, 2191 (1974). (c) For other examples of additions of N-centered radicals (derived from *N*-chloro amines) to olefins, see F. Minisci, *Acc. Chem. Res.*, **8,** 165 (1975); R. Furstoss, G. Esposito, P. Teissier, and B. Waegell, *Bull. Soc. Chim. Fr.*, 2485 (1974).
(6) A Calder, A. R. Forrester, and S. P. Hepburn, *Org. Synth.*, **52,** 77 (1972).
(7) This same reducing system was also employed to prepare the hydroxylamine **16.** See ref 5a.
(8) This relatively low isolated yield is attributable to the difficulties in isolating the hydrolytically and thermally unstable liquid benzoate **24b.** NMR analysis of the reaction mixture indicated that hydroxylamine **24a** is the major product formed from **20.**
(9) For examples, see (a) T. R. Juneja and H. Dannenberg, *Tetrahedron,* **31,** 695, 701 (1975); (b) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, pp 2–3 and 10–11.
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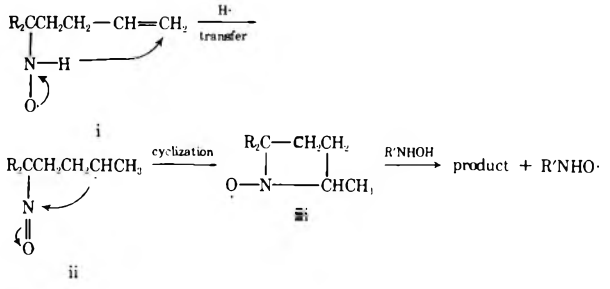
(11) (a) T. A. J. W. Wajer, A. Mackor, and T. J. deBoer, *Tetrahedron,* **25,** 175 (1969). (b) D. F. Bowman, J. L. Brokenshire, T. Gillan, and K. U. Ingold, *J. Am. Chem. Soc.*, **93,** 6551 (1971). (c) A referee has suggested that the ring-closure step, rather than involving the radical addition to an olefin indicated in structure **37,** involves an initial H atom transfer I to yield an intermediate nitroso radical II that cyclizes to III. Although the second step, II → III, in this sequence would clearly be favorable, we

are unaware of precedent for the first step, i → ii, the transfer of an H· atom from a radical to a double bond. Consequently, we presently prefer the radical addition mechanism (**37** in Scheme VII) for which some precedent exists (ref 5b,c) but have no experimental basis for excluding the alternative radical chain process involving i → ii → iii.



(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 NMR spectrometer and the ^{13}C NMR spectra were obtained with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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(23) (a) An $E_{1/2}$ value of −1.36 V vs. SCE has been reported for *t*-BuNO in acetonitrile solution: H. Sayo, Y. Tsukitani, and M. Masui, *Tetrahedron*, **24**, 1717 (1968). (b) The reduction of PhNO in aqueous solutions of varying pH has been studied polarographically (ref 10) and the reduction of PhNO in aprotic solvents has been studied by cyclic voltammetry [M. R. Asirvatham and M. D. Hawley, *Electroanal. Chem., Interfacial Electrochem.*, **57**, 179 (1974)].

(24) The shift of $E_{1/2}$ to more negative potentials with increasing pH has also been observed in the polarographic oxidation of PhNHOH. See ref 10.

(25) These conditions for the polarographic determination of *N*-alkylhydroxylamines were described by P. E. Iverson and H. Lund, *Anal. Chem.*, **41**, 1322 (1969). These authors report an $E_{1/2}$ value of −0.47 V vs. SCE for *t*-BuNHOH.

A New Synthesis of 2-Alkylpyrrolidines and 2-Alkylpiperidines[1]

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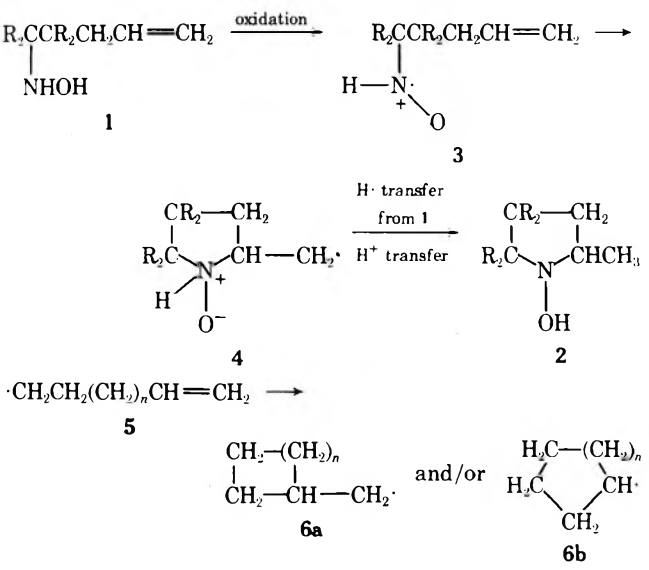
Each of the *N*-(4-pentenyl)hydroxylamine derivatives **7** and **17** underwent facile cyclization to the 2-methylpyrrolidine derivatives **10** and **18** when the starting materials were warmed briefly to 50–60 °C. Subsequently reduction and acetylation with Zn, HOAc, and Ac_2O afforded the corresponding amides **12** and **19**. Cyclization of the homologous *N*-(5-hexenyl)hydroxylamines **27** and **34** to the 2-methylpiperidine derivatives **28** and **35** (isolated after conversion to the amides **29** and **22**) required higher temperatures (130–140 °C) and longer reaction times (1–2 h). Attempts to cyclize the unsaturated hydroxylamines **38** and **39** were unsuccessful. The ease and direction of these various cyclizations, believed to be radical chain reactions, parallels the behavior of related alkenyl carbon radicals **5**.

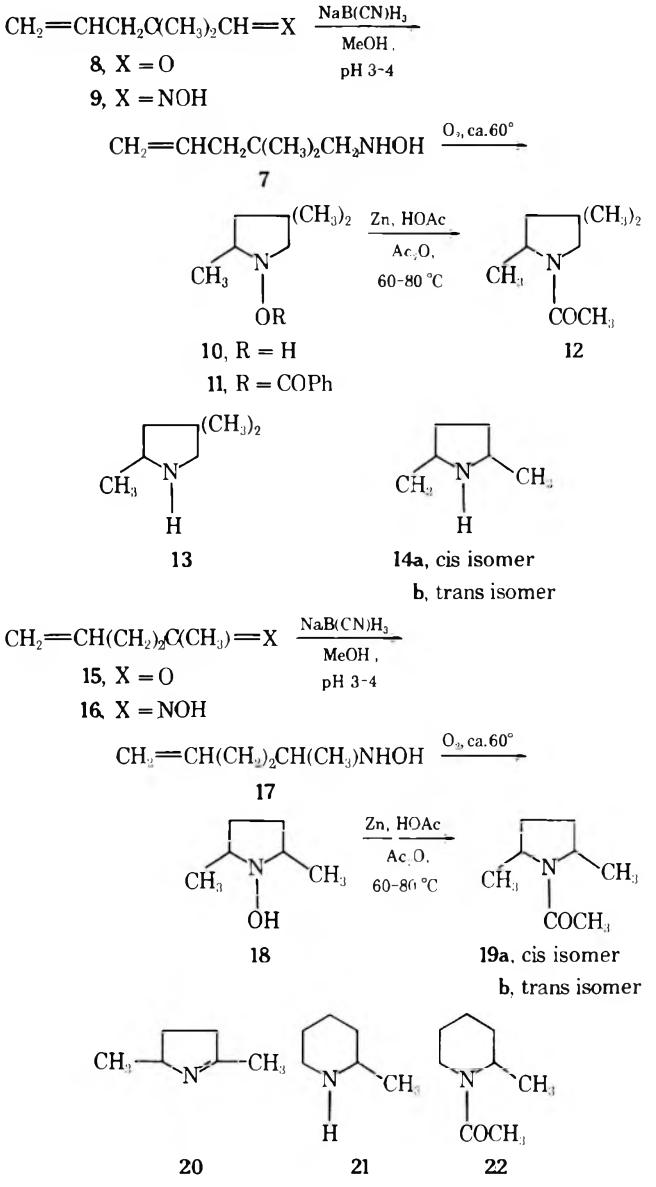
In an accompanying paper[2] we have described a study of the cyclization of certain unsaturated hydroxylamines **1** (Scheme I) to the corresponding *N*-hydroxypyrrolidines **2**. We believe this cyclization to be a radical chain process involving the intermediate radicals **3** and **4** in which the step **3** → **4** is analogous to the cyclization **5** → **6** of certain carbon radicals **5**.[3–5] In the previous study[2] the synthetic attractiveness of the cyclization **1** → **2** was mitigated by the facts that synthesis of the starting hydroxylamines **1** by selective reduction of the corresponding nitro olefins was tedious and isolation of the thermally unstable, easily oxidized cyclic hydroxylamines **2** was difficult. In this paper we describe alternative procedures that overcome these problems.

An especially simple and efficient synthesis of unsaturated hydroxylamine derivatives, e.g., **7** (Scheme II), from the corresponding unsaturated carbonyl compounds **8** utilized the selective reduction of the oxime **9** with $NaB(CN)H_3$ in acidic MeOH.[6] Although the original procedure recommended[6a] performing the reaction at pH 4 (bromocresol blue indicator), we found the reduction of ketox-

Scheme I



Scheme II

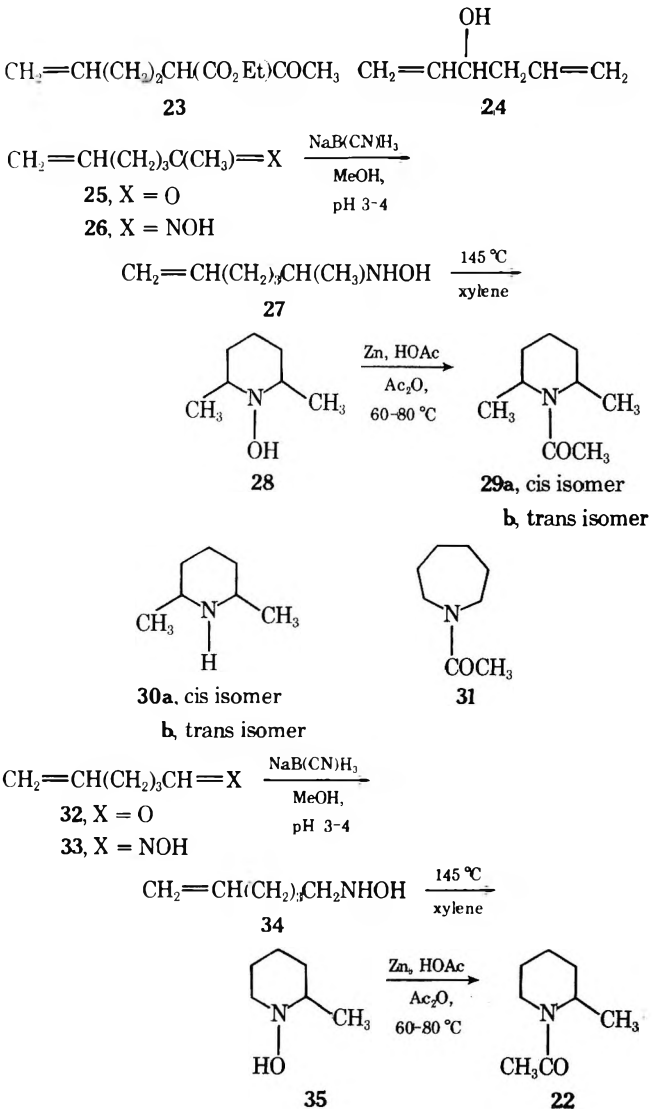


imes at this pH to be rather slow and recommend use of a reaction mixture at pH 3–4 (methyl orange indicator). For our purposes the reduction of the unsaturated oximes to hydroxylamines with BH_3 in THF[7] was not a suitable alternative because of a competing reaction of the olefin with BH_3. Although the reductions of oximes **9** and **16** with $NaB(CN)H_3$ produced solutions of the unsaturated hydroxylamines **7** and **17**, even brief warming of these intermediates during product isolation, like previously studied *N*-(4-pentenyl)hydroxylamine derivatives,[2] resulted in cyclization to form the pyrrolidine derivatives **10** and **18**.

Although NMR analysis indicated that pyrrolidine **10** was the major, if not exclusive, product obtained on cyclization of **7**, the isolation of pure samples of either the water-soluble, easily oxidized hydroxylamine **10** or its thermally unstable benzoyl derivative **11** was not satisfactory procedures. Consequently, we subjected the crude cyclized products **10** and **18** to reduction with Zn in a mixture of HOAc and Ac_2O in order to produce the more easily isolated acetamide derivatives **12** and **19**. Although both the intermediate hydroxylamine **18** (NMR analysis) and the final amide **19** were mixtures of stereoisomers, we presume that the composition of the final isolated product (ca. 35% **19a** and 65% **19b**) does not necessarily reflect the stereoisomeric composition of the intermediate hydroxylamine **18** because the imine **20** is a probable intermediate in the reduction process. By use of an authentic sample of the isomeric piperidine derivative **22**, we demonstrated that the amounts of this six-membered cyclic product present were below the limits we could detect by GLC analysis. Consequently, cyclization of the nitroxide radical from **17**, like the analogous carbon radical **5** (n = 2),[3] proceeds to form predominantly, if not exclusively, a five-membered ring (analogous to **6a**, n = 2) rather than a six-membered ring (analogous to **6b**, n = 2). The overall yields of the amides **12** and **19**, based on the starting oximes, were 51 and 65%, respectively.

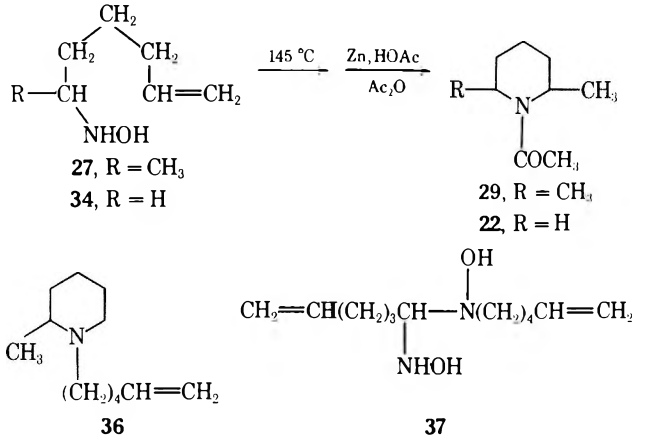
To explore the use of this free-radical cyclization reaction for the preparation of six-membered rings, the two oximes **26** and **33** (Scheme III) were reduced with $NaB(CN)H_3$ to form the unsaturated hydroxylamines **27** and **34**. The cyclization of these materials **27** and **34** was clearly less facile than cyclization of the lower homologues **7** and **17** since the hydroxylamines **27** and **34** could be isolated after solutions containing them had been heated on a steam bath to remove solvents. Cyclization of these intermediates **27** and **34** was accomplished by adding them in xylene solution to refluxing xylene (ca. 145 °C) under high-dilution conditions. Although cyclization was observed when the hydroxylamines **27** and **34** were heated to 160 °C without solvent, various by-products were formed under these conditions. Application of the Zn–HOAc–Ac_2O re-

Scheme III



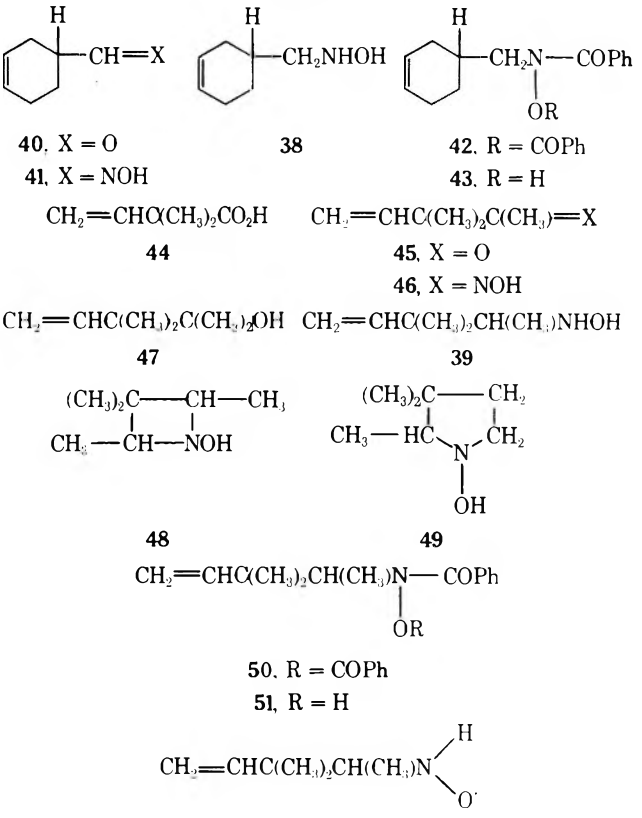
duction procedure to the two crude cyclic products **28** and **35** yielded the amides **29** (mainly the trans isomer **29b**) and **22**. By use of an authentic sample of the amide **31**, we were able to demonstrate that the cyclization of hydroxylamine **34** and subsequent reduction yielded the six-membered ring product **22** with none of the seven-membered ring product **31** being detected by our GLC analysis. Both the slower rates of cyclization of nitroxides from **27** and **34** compared to the nitroxides from **7** and **17** and the cyclizations to form six- rather than seven-membered products are again in accord with studies of analogous carbon-centered radicals **5** (n = 3).[3,8] These observations are also in agreement with the observation that N-centered radicals (from N-chloro amides) were successfully cyclized to form five-membered rings but not the isomeric six-membered rings.[5d] The overall yields of amides **22** and **29**, based on the starting oximes, were ca. 28 and 40%, respectively.

Although the cyclization of the hydroxylamine **27** under high-dilution conditions followed by reduction and acetylation yielded the amide **29b** accompanied by only minor amounts of by-products, the analogous reactions with the hydroxylamine **34** formed both the amide **22** and several by-products even when the cyclization was performed under high-dilution conditions. The principal by-products obtained from hydroxylamine **34** were mixtures of higher molecular weight materials and a volatile by-product shown to be amine **36**. While the origin of this by-product **36** is uncertain, it may result from a bimolecular reaction of the hydroxylamine **34** with the oxime **33** (from oxidation of **34**) to form a bimolecular product such as **37** that undergoes cyclization and reduction. In any event, it is apparent that the cyclization is facilitated by the methyl substituent present in **27** but not **34**. The ability of alkyl substituents to facilitate ring closures (the Thorpe–Ingold effect) has been noted previously in cyclization of derivatives of the carbon radical **5** (n = 2).[9]



To further explore the scope of this cyclization, we examined the hydroxylamines **38** and **39** (Scheme IV). After the hydroxylamine **38** (characterized as the hydroxamic acid **43**) had been heated to 170 °C for 1 h, we could discern no evidence of cyclization (NMR analysis) suggesting that the extra strain involved in forming either of the two possible bicyclic hydroxylamines was sufficient to prevent cyclization. The hydroxylamine **39**, obtained by the usual reduction of the oxime **46**, was characterized as the crystalline hydroxamic acid **51**. Heating the hydroxylamine **39** under a variety of conditions failed (NMR analysis) to form either of the cyclized products **48** or **49**. Instead, the hydroxylamine **39** was partially converted to the oxime **46** by oxidation to the nitroxide **52** which failed to cyclize and underwent disproportionation to form the oxime. This observation is again compatible with the behavior of the corresponding carbon radical **5** (n = 1) where cyclization (to form **6b**, n = 1) usually is not observed.[3] In the previously mentioned study[5d] of the photochemically induced cyclization of N-chloro amides, the N-centered radical analogous to that derived from hydroxylamine **38** did cyclize but the radical analogous to the nitroxide from hydroxylamine **39** failed to undergo cyclization.

Scheme IV



Experimental Section[10]

Preparation and Cyclization of the Hydroxylamine 17. Reaction of 49 g (0.50 mol) of the ketone **15** (Aldrich Chemical Co.), with a refluxing solution of 104 g (1.50 mol) of $HONH_3Cl$, 123 g (1.50 mol) of NaOAc, and 20 ml of EtOH in 500 ml of H_2O for 40 h yielded 44.4 g (88%) of the oxime **16** as a colorless liquid: bp 64–66 °C (2.5 mm), n^{25}D 1.4632 [lit. bp 187,[11a] 190 °C[11b]]; ir (CCl_4) 3580, 3250 (OH), 1640 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.67 (1 H, broad s, OH), 4.8–6.2 (3 H, m, vinyl CH), 2.1–2.7 (4 H, m, CH_2), and 1.83 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 113 (M^+, 11), 112 (9), 98 (35), 96 (35), 81 (35), 73 (40), 55 (89), 54 (70), 53 (32), 43 (20), 42 (100), 41 (85), and 39 (63). The product exhibits two GLC peaks (Carbowax 20M on Chromosorb P) with retention times of 14.0 (ca. 8%) and 21.2 min (ca. 92%) that presumably correspond to the two geometrical isomers of oxime **16**.

To a solution of 5.65 g (50 mmol) of the oxime **16**, 3.4 g (54 mmol) of $NaB(CN)H_3$, and 1 mg of methyl orange in 50 ml of MeOH was added, dropwise and with stirring, a mixture (1:1 v/v) of MeOH and aqueous 12 M HCl. The rate of addition was controlled so that the color of the reaction mixture remained reddish-orange (pH 3–4)[6] for a period of 1 h. Then the solution was concentrated under reduced pressure, made basic by the addition of aqueous 6 M KOH, and extracted with Et_2O. The ethereal extract was dried (K_2CO_3) and concentrated in a water bath (50–70 °C) to leave 5.54 g of crude liquid hydroxylamine **18**. From two comparable reactions where the reduction was effected either at pH 3–4 (methyl orange indicator) for 1 h or at pH 4–5 (bromocresol blue indicator)[6a] for 5 h, the crude liquid product (83–95% yield) was found to contain (NMR analysis) mainly the stereoisomers of the cyclic hydroxylamine **18**: NMR (CCl_4) δ 7.63 (ca. 1 H, broad s, OH), 1.2–3.5 (ca. 6 H, m, aliphatic CH), and two doublets (J = 6.5 Hz) at 1.18 (minor) and 1.13 (major) (ca. 6 H, CH_3 groups of stereoisomers of **18**). When the crude product was not heated during concentration of the solvents, the NMR spectrum of the crude

product also exhibited a multiplet in the region δ 4.8–6.2 (vinyl CH) suggesting that the cyclization 17 → 18 was incomplete.

The crude hydroxylamine 18 (5.54 g) from the above experiment was dissolved in a mixture of 20.4 g (0.20 mol) of Ac_2O and 18 g (0.30 mol) of HOAc and then 14.0 g (0.15 g-atom) of Zn dust was added, portionwise with vigorous stirring during 30 min. The reaction mixture, whose temperature rose to 100 °C during the addition of the Zn, was cooled to 70 °C and then stirred at 60–70 °C for an additional 3 h. The resulting mixture was filtered and the residue was washed thoroughly with Et_2O. The combined filtrate and washings were concentrated under reduced pressure and then made basic (aqueous NaOH) and continuously extracted with Et_2O. After the ethereal extract had been dried and concentrated, distillation of the residual liquid (6.3 g) separated 4.58 g (65%) of a mixture of the stereoisomers of amide **19** as a colorless liquid: bp 61–66 °C (1 mm); $n^{25}D$ 1.4662; ir (CCl_4) 1645 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.3 (2 H, m, CHN), 1.3–2.4 (7 H, m, CH_2 including a CH_3CO singlet at 1.92), and three overlapping doublets (J = 6.5 Hz) at 1.22, 1.17, and 1.10 (6 H, CH_3 of stereoisomeric amides); mass spectrum m/e (rel intensity) 141 (M^+, 66), 126 (35), 99 (38), 98 (18), 85 (23), 84 (100), 67 (19), 57 (25), 43 (69), 42 (35), and 41 (28). The product exhibited two GLC peaks (Carbowax 20M on Chromosorb P) with retention times of 32.9 (ca. 35%) and 34.8 min (ca. 65%) attributable to the cis (**19a**) and trans (**19b**) isomers of amide **19**. However, no peak was observed at 46.4 min, the retention time of the structurally isomeric amide **22**.

To obtain an authentic sample of the amide **19**, a cold (5 °C) solution of 500 mg (5.05 mmol) of the amine **14** (a mixture of stereoisomers obtained from Aldrich Chemical Co.) and 2.0 g of Et_3N in 10 ml of PhH was treated with 2.0 g of CH_3COCl. After the resulting mixture had been allowed to stand for 30 min, it was partitioned between aqueous 6 M KOH and Et_2O, and the ethereal layer was dried and concentrated. Distillation of the residual liquid in a short-path still separated 249 mg (35%) of the crude amide **19**. A pure sample of the mixture of amide **19** stereoisomers was collected (GLC) as a colorless liquid, $n^{25}D$ 1.4647, that contained (GLC, 8-m column of TCEP on Chromosorb P) the cis amide **19a** (ca. 64%, 138.0 min) and the trans amide **19b** (ca. 36%, 147.2 min).

To complete the characterization of the amides **19**, the mixture of amines **14**[12] (Aldrich Chemical Co.) was separated by collection from GLC (8-m column packed with Carbowax 20M on base-washed Chromosorb P). The retention times follow: cis amine **14a**, 53.0 min; trans amine **14b**, 59.8 min. The collected cis amine **14a** formed a picrate as yellow needles from PhH, mp 118–119 °C (lit.[12] mp 116–118 °C), and the collected trans amine **14b** formed a picrate as yellow needles from PhH, mp 130–131 °C (lit.[12] mp 126–127, 130–131 °C). Reaction of 0.13 g of the cis amine **14a** with excess Ac_2O in pyridine for 2 h followed by separation of the neutral material gave 196 mg of crude product. A collected (GLC, Carbowax 20M on Chromosorb P) sample of the pure cis amide **19a** (yield 90 mg or 42%) was obtained as a colorless liquid: $n^{25}D$ 1.4649; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.3 (2 H, m, CHN), 1.5–2.4 (7 H, m, aliphatic CH including a CH_2CO singlet at 1.97), and 1.25 (6 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 21), 126 (9), 99 (11), 84 (100), and 43 (21).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.04; H, 10.72; N, 9.85.

After reaction of 0.16 g of the trans amine **14b** with excess Ac_2O in pyridine, the crude neutral product was separated and 135 mg (51%) of the trans amide **19b** was collected (GLC) as a colorless liquid: $n^{25}D$ 1.4700; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.7–4.4 (2 H, m, CHN), 1.4–2.4 (7 H, m, aliphatic CH including a CH_3CO singlet at 1.97), 1.21 (3 H, d, J = 6.5 Hz, CH_3), and 1.15 (3 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 55), 126 (34), 99 (20), 98 (18), 85 (20), 84 (100), 43 (64), 42 (33), and 41 (23).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.02; H, 10.74; N, 9.85.

When mixtures of the two stereoisomeric amides **19** were subjected to GLC analysis (8-m column packed with TCEP on Chromosorb P), the retention times were as follows: cis amide **19a**, 155 min, and trans amide **19b**, 165 min. Comparison of the GLC retention times and ir, NMR, and mass spectra of the mixture of amides **19** obtained from the hydroxylamine **18** with the corresponding data for the pure amides **19a** and **19b** allowed us to confirm the identities of the amide products.

To obtain an authentic sample of the amide **22**, 10.1 g (102 mmol) of 2-methylpiperidine (**21**, Aldrich Chemical Co.) was treated with 11.0 g (108 mmol) of Ac_2O and the resulting mixture was stirred for 1 h. Then 20 ml of aqueous 6 M KOH was added, stirring was continued for 30 min, and the mixture was extracted with Et_2O. After the ethereal extract had been washed with aqueous 3 M HCl, dried, and concentrated, distillation separated 9.09 g (64%) of the amide **22**, bp 75–79 °C (2 mm). This sample was washed with aqueous 5% NaOH, dried, and redistilled to afford 5.9 g of the pure amide **22** as a colorless liquid: bp 88–89 °C (2.5 mm), $n^{25}D$ 1.4785 [lit. bp 55–56 °C (0.15 mm),[13a] 86.5–87.5 °C (3.5 mm)[13b]]; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.2–4.5 (3 H, m, CH_2N and CHN), 1.93 (3 H, s, $COCH_3$), 1.3–1.9 (6 H, m, CH_2), and 1.15 (3 H, d, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 141 (M^+, 20), 126 (18), 84 (100), 70 (11), 57 (10), 56 (22), 55 (10), 43 (49), 42 (20), and 41 (14).

Preparation of the Oxime 26. To a solution of the Na enolate, prepared from 47 g (0.36 mol) of ethyl acetoacetate, 8.7 g (0.38 g-atom) of Na, and 125 ml of EtOH, was added, dropwise and with stirring during 2 h, 50 g (0.37 mol) of 4-bromo-1-butene. The resulting mixture was refluxed with stirring for 1 h and then cooled, filtered, and concentrated. Fractional distillation of the residual liquid separated 33.5 g (51%) of the alkylated β-keto ester **23** as a colorless liquid: bp 111–116 °C (15 mm), $n^{25}D$ 1.4402 [lit.[14] bp 103–110 °C (22 mm)]; ir (CCl_4) 1740 (ester C=O), 1720 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 4.15 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.33 (1 H, t, J = 6.5 Hz, COCHCO), 1.7–2.3 (7 H, m, CH_2 including a CH_3CO singlet at 2.12), and 1.25 (3 H, t, J = 7 Hz, ethoxyl CH_3); mass spectrum m/e (rel intensity) 184 (M^+, 2), 130 (26), 73 (21), 55 (40), and 43 (100). A mixture of 33 g (179 mmol) of the β-keto ester **23** and 400 ml of aqueous 5% NaOH was refluxed with stirring for 10 h and then cooled and extracted with Et_2O. The ethereal solution was dried and fractionally distilled to separate 15.7 g (79%) of the ketone **25** as a colorless liquid: bp 72–73 °C (50 mm), $n^{25}D$ 1.4240 [lit.[14] bp 71–73 °C (50 mm), $n^{25}D$ 1.4223]; ir (CCl_4) 1720 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 2.37 (2 H, t, J = 6.5 Hz, CH_2CO), and 1.3–2.2 (7 H, m, CH_2 including a CH_3CO singlet at 2.00); mass spectrum m/e (rel intensity) 112 (M^+, 17), 94 (10), 58 (72), 55 (12), 43 (100), 42 (22), and 39 (10). The product exhibited a single peak on GLC analysis (silicone SE-30 on Chromosorb P). Our attempts to prepare this ketone **25** by the vapor phase pyrolysis (Cope rearrangement) of 3-methyl-1,5-hexadien-3-ol (from CH_2=$CHCOCH_3$ and CH_2=$CHCH_2MgBr$) in a tube heated to 400–450 °C resulted in the formation of a mixture (NMR and GLC analysis, $AgNO_3$ in Carbowax 20M on Chromosorb P) of the desired ketone **25** (ca. 64%, retention time 49.6 min) and three other components: 31.2 min, ca. 11%; 40.0 min (ca. 19%); and 54.2 min (ca. 1%). The second most abundant component in the mixture (a methyl ketone, ir and NMR analysis) is believed to be methyl 2-methylcyclobutyl ketone formed by thermal rearrangement of the ketone **25**.[15]

To a cold (5 °C) mixture of 15.0 g (134 mmol) of the ketone **25**, 14 g (0.20 mol) of $HONH_3Cl$, and 60 ml of H_2O was added, dropwise and with stirring during 20 min, a solution of 9.9 g (94 mmol) of Na_2CO_3 in 80 ml of H_2O.[16] After the reaction mixture had been stirred in an ice bath for 1 h, and at 25 °C for 1 h, it was extracted with Et_2O and the ethereal extract was dried and concentrated. Distillation of the residual liquid separated 16.2 g (96%) of the oxime **26** as a colorless liquid: bp 73–75 °C (2 mm), $n^{25}D$ 1.4652; ir (CCl_4) 3580, 3230 (OH), 1640 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.5 (1 H, broad s, OH), 4.7–6.2 (3 H, m, CH=CH_2), and 0.9–2.6 (9 H, m, CH_2 including a CH_3C=N singlet at 1.82); mass spectrum m/e (rel intensity) 127 (M^+, 15), 112 (24), 86 (10), 73 (100), 69 (10), 68 (12), 67 (11), 55 (44), 42 (36), 41 (47), and 39 (32).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.20; H, 10.33; N, 10.94.

Preparation and Cyclization of the Hydroxylamine 27. A solution of 674 mg (5.3 mol) of the oxime **26**, 346 mg (5.5 mmol) of $NaB(CN)H_3$, and cresol blue indicator in 20 ml of MeOH was treated with a 6 M HCl solution in H_2O–MeOH during 5 h to maintain a yellow (pH 4) reaction solution and then subjected to the previously described isolation procedure to yield 596 mg (86%) of the crude solid hydroxylamine **27**, mp 38–42 °C. The crude hydroxylamine **27** was sublimed under reduced pressure to give the pure hydroxylamine 27 as colorless needles: mp 42–44 °C; ir (CCl_4) 3590, 3230 (OH, NH), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 6.29 (2 H, s, OH, NH), 4.8–6.2 (3 H, m, CH=CH_2), 2.7–3.2 (1 H, m, CHN), 1.2–2.3 (6 H, m, CH_2), and 1.07 (3 H, d, J = 6 Hz, CH_3); mass spectrum m/e (rel intensity) 129 (M^+, 14), 114 (100), 98 (11), 81 (13), 70 (14), 69 (12), 60 (33), 56 (15), 55 (41), 44 (24), 43 (26), 42 (73), 41 (53), and 39 (31).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.19; H, 11.72; N, 10.78.

In a subsequent experiment 3.8 g (30 mmol) of the oxime **26** in 50 ml of MeOH was reduced with 2.20 g (35 mmol) of $NaB(CN)H_3$ at pH 3–4 (methyl orange indicator) for 1 h to give 3.9 g of the crude hydroxylamine **27**. A solution of this hydroxylamine in 25 ml of xylene was added, dropwise during 40 min through a high-dilution head,[17] to 25 ml of refluxing xylene. After the addition was complete, the solution was concentrated and the crude cyclic hydroxylamine **28** (NMR analysis) was reduced with 5.9 g (90 mg-atoms) of Zn, 12.2 g (120 mmol) of Ac_2O, and 10.8 g (180 mmol) of HOAc following previously described reaction and isolation procedures. Distillation of the crude liquid product (2.6 g) separated 1.84 g (40%) of the trans amide **29b** as a colorless liquid, bp 85–90 °C (1.5 mm), $n^{25}D$ 1.4788. Comparison of the GLC retention times and ir and NMR spectra of this product with the subsequently described samples of amide **29** established that this material was the trans amide **29b**. In another experiment where 2.35 g (18.5 mmol) of the oxime **26** was reduced with $NaB(CN)H_3$ and the crude hydroxylamine **27** was heated to 160 °C for 1 h with no solvent, subsequent reduction with Zn, Ac_2O, and AcOH yielded 42% of a crude product containing (GLC, Carbowax 20M on Chromosorb P) the amide **29** (ca. 85%, retention time 52.0 min) accompanied by several minor unidentified impurities: 9.0 min, ca. 3%; 11.6 min, ca. 2%; 14.0 min, ca. 1%; 46.4 min, ca. 4%; and 61.2 min, ca. 5%.

To obtain an authentic sample of this cis amide **29a**, a mixture of 11.3 g (0.10 mol) of the cis amine **30a**[18] (Aldrich Chemical Co.) and 12 g of Ac_2O was stirred for 1 h and then treated with 20 ml of aqueous 6 M KOH and extracted with Et_2O. The ethereal extract was washed with aqueous 3 M HCl, dried, concentrated, and distilled to separate 4.07 g (26%) of the cis amide **29a** as a colorless liquid: bp 83–86 °C (3.5 mm), $n^{25}D$ 1.4772 [lit.[13a] bp 62–63 °C (0.15 mm), $n^{25}D$ 1.4785]; ir (CCl_4) 1645 cm^{-1} (amide C=O); NMR (CCl_4) δ 4.1–4.7 (2 H, m, CHN), 1.97 (3 H, s, CH_3CO), 1.4–1.9 (6 H, m, CH_2), and 1.22 (6 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 155 (M^+, 24), 140 (18), 112 (14), 98 (100), 70 (21), 43 (32), and 42 (17).

Following a previously described procedure,[18] a solution of 50 g (0.47 mol) of 2,6-dimethylpyridine in 800 ml of anhydrous EtOH was reduced by the portionwise addition of 86 g (3.74 g-atoms) of Na. The crude basic product was separated and distilled to give 29 g (55%) of colorless liquid, bp 131–139 °C (lit.[18] bp 125–132 °C) that contained (GLC, 8-m column packed with Carbowax 20M on base-washed Chromosorb P) the cis amine **30a** (ca. 47%, retention time 15.2 min), the trans amine **30b** (ca. 21%, 19.2 min), a material believed to be a tetrahydropyridine (ca. 20%, 26.0 min), and the starting 2,6-dimethylpyridine (ca. 12%, 34.8 min). Samples of the pure trans amine **30b** were collected (GLC) from the mixture as a colorless liquid with NMR absorption corresponding to the published spectrum.[18] Reaction of 150 mg of this trans amine **30b** with excess PhCOCl in pyridine followed by separation of the crude neutral material and crystallization from cold hexane afforded 106 mg (37%) of the *N*-benzoyl derivative of amine **30b** as colorless needles, mp 53–55 °C. Recrystallization sharpened the melting point of this benzamide to 54–55 °C (lit.[19] mp 54–55 °C); ir (CCl_4) 1650 cm^{-1} (amide C=O); NMR (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 3.6–4.1 (2 H, m, CHN), and 1.0–2.0 (12 H, m, aliphatic CH including a CH_3 doublet, J = 7 Hz, at 1.23); mass spectrum m/e (rel intensity) 217 (M^+, 15), 205 (16), 105 (100), and 77 (30). A 70-mg sample of the collected trans amine **30b** was treated with picric acid in PhH to yield 200 mg (99%) of the picrate of the trans amine **30b** as yellow needles, mp 144–146 °C.[20]

A collected (GLC) sample of the trans amine **30b** was treated with excess Ac_2O in pyridine and the crude neutral product was separated in the usual way. A pure sample of the trans amide **29b** was collected (GLC, Carbowax 20M on Chromosorb P) as a colorless liquid: $n^{25}D$ 1.4800; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.8–4.3 (2 H, m, CHN) and 1.0–2.2 (15 H, m, aliphatic CH including a CH_3CO singlet at 1.95 and a CH_3 doublet, J = 7 Hz, at 1.20); mass spectrum m/e (rel intensity) 155 (M^+, 15), 140 (18), 98 (100), 70 (25), 55 (25), 44 (30), 43 (75), 42 (38), and 41 (35).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.58; H, 11.07; N, 9.01.

The two stereoisomeric amides were partially resolved on an 8-m GLC column packed with TCEP on Chromosorb P. The retention times follow: trans amide **29b**, 300 min; and cis amide **29a**, 313 min.

Preparation of the Oxime 33 The previously described[21] reaction of CH_2=$CHCH_2MgBr$ with acrolein yielded 43% of the alcohol **24** as a colorless liquid: bp 50–52 °C (25 mm), $n^{25}D$ 1.4458 [lit.[21] bp 42–48 °C (17 mm)]; ir (CCl_4) 3590, 3400 (OH), 1645 (C=C), and 930 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.2 (6 H, m, CH=CH_2), 3.8–4.3 (1 H, m, CHO), 3.17 (1 H, broad, OH, exchanged with D_2O), and 2.1–2.5 (2 H, m, allylic CH_2); mass spectrum m/e (rel intensity) 57 (100), 55 (6), 43 (5), 42 (6), 41 (10), and 39 (14). The alcohol **24** (57 g or 0.58 mol) was rearranged by passing it through a tube packed with glass beads and heated to 410 °C as previously recommended.[22] Distillation of the pyrolysate separated 23.8 g (42%) of the aldehyde **32** as a colorless liquid: bp 128–129 °C, $n^{25}D$ 1.4236 (lit. bp 120–121,[22] 118–118.5,[23] 118–121 °C,[14] $n^{20}D$ 1.395,[22] 1.4109,[23] 1.4113[14]). The product exhibited one major GLC peak (Carbowax 20M on Chromosorb P) at 10.0 min with minor peaks at 5.8 (ca. 1%, unidentified impurity) and 20.4 min (ca. 2%, alcohol **24**) and had the following spectral properties: ir (CCl_4) 2690, 2790 (aldehyde CH), 1725 (C=O), 1640 (C=C), and 910 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.75 (1 H, t, J = 1.3 Hz, CHO), 4.7–6.2 (3 H, m, CH=CH_2), and 1.4–2.6 (6 H, m, CH_2); mass spectrum m/e (rel intensity) 98 (M^+, 2), 81 (40), 57 (20), 55 (41), 54 (100), 44 (20), 42 (31), 41 (75), and 39 (58).

A solution of 15.3 g (144 mmol) of Na_2CO_3, 20.1 g (205 mmol) of the aldehyde **32**, and 21.3 g (307 mmol) of $HONH_3Cl$ in 300 ml of H_2O was stirred in an ice bath for 1 h and at 25 °C for 14 h. After the usual isolation procedure, distillation separated the oxime **33** as 20.2 g (87.4%) of colorless liquid: bp 63–64 °C (2 mm), $n^{25}D$ 1.4612; ir (CCl_4) 3590, 3260 (OH), 1640 (C=N, C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.50 (1 H, broad, OH, exchanged with D_2O), two triplets (J = 6 Hz) at 7.32 and 6.63 (total 1 H, CH=N of syn and anti isomers), 4.7–6.2 (3 H, m, CH=CH_2), and 1.3–2.6 (6 H, m, CH_2); mass spectrum m/e (rel intensity) 113 (M^+, 5), 98 (16), 59 (100), 55 (40), 41 (64), and 39 (41).

Anal. Calcd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.39. Found: C, 63.61; H, 9.82; N, 12.28.

Preparation and Cyclization of the Hydroxylamine 34. Reduction of 5.65 g (50 mmol) of the oxime **33**, with 3.36 g (55 mmol) of $NaB(CN)H_3$ in 50 ml of MeOH containing methyl orange at 25 °C for 1 h with periodic addition of 6 M HCl in H_2O–MeOH yielded 5.31 g (93%) of the crude hydroxylamine **34** (NMR analysis) as a liquid that solidified on cooling. A solution of this hydroxylamine **34** in 35 ml of xylene was added dropwise during 30 min to 35 ml of refluxing xylene and the resulting solution was refluxed for an additional 1 h and then concentrated under reduced pressure. A solution of the residual crude hydroxylamine **35** (NMR analysis) was reduced with 9.8 g (0.15 g-atom) of Zn, 20 g (0.20 mol) of Ac_2O, and 18 g (0.30 mol) of HOAc at 70–80 °C for 9 h. After the usual isolation procedure, distillation separated 2.427 g of fractions, bp 73–81 °C (2.5 mm), $n^{25}D$ 1.4705–1.4770, containing (GLC, Carbowax 20M on Chromosorb P) 70–98% of the amide **22** (retention time 36.4 min, total yield ca. 27%), accompanied by 2–30% of several impurities (6.4, 7.6, and 10.8 min). The major by-product was the subsequently identified amine **36** (retention time 10.8 min). However, the GLC curve did not exhibit a peak at 52.5 min, the corresponding retention time for the isomeric amide **31**. A distillation fraction, bp 79–81 °C (2.5 mm), $n^{25}D$ 1.4770, containing (GLC) >98% of the amide **22** was identified with the previously described sample by comparison of ir, NMR, and mass spectra and GLC retention times.

In another experiment 2.07 g (18.3 mmol) of the oxime **33** was reduced and the crude hydroxylamine product **34** (2.13 g) was heated to 140 °C for 20 min without solvent. After reduction with Zn and acetylation, distillation of the crude product gave 468 mg of a lower boiling fraction [bp 72–85 °C (2.5 mm), $n^{25}D$ 1.4635] containing (NMR analysis) mainly the amine **36** and 463 mg of a fraction [bp 85–160 °C (2.5 mm), $n^{25}D$ 1.4730] that contained (NMR analysis) mainly the amide **22**. To explore the effect of high dilution, a solution of 6.7 g of the crude hydroxylamine **34** (from reduction of 6.35 g or 50 mmol of the oxime) in 25 ml of xylene was added, dropwise through a high-dilution head[17] during 2 h, to 150 ml of refluxing xylene. After the resulting mixture had been refluxed for 4 h it was concentrated by fractional distillation and the residual crude liquid (3.9 g) was reduced in the usual way with 13.1 g (0.2 g-atom) of Zn dust, 25.5 g of Ac_2O, and 24.8 g of HOAc. Distillation of the resulting crude product separated 2.60 g of colorless liquid, bp 73–94 °C (1 mm), $n^{25}D$ 1.4725, that contained (GLC and NMR analysis) the amide **22** (ca. 75% of the mixture, retention time 14.8 min, yield ca. 28%), the amine **36** (ca. 21% of the mixture, 4.4 min), and a minor unidentified impurity (ca. 4%, 26.8 min).

To obtain an authentic sample of the amide **31**, a solution of 9.9 g (0.10 mol) of hexamethylenimine (Aldrich Chemical Co.) in 15 g (0.15 mol) of Ac_2O was stirred at 25°C for 16 h, and then subjected to the usual isolation procedure. Distillation separated 1.70 g (11%)

of the amide 31 as a colorless liquid: bp 88–93 °C (2 mm), n^{25}D 1.4822 [lit.[24] bp 113–115 °C (8 mm), n^{25}D 1.4890]; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 3.2–3.6 (4 H, m, CH_2N), 1.95 (3 H, s, CH_3CO), and 1.3–1.9 (8 H, m, CH_2); mass spectrum *m/e* (rel intensity) 141 (M^+, 31), 98 (23), 84 (32), 70 (38), 57 (28), 56 (44), 44 (30), 43 (100), 42 (30), and 41 (27).

A collected (GLC) sample of the by-product, amine **36**, was obtained as a colorless liquid: n^{25}D 1.4632; ir (CCl_4) 1640 (C=C) and 915 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 1.2–3.0 (17 H, m, aliphatic CH), and 1.00 (3 H, d, J = 6 Hz, CH_3); mass spectrum *m/e* (rel intensity) 181 (M^+, 6), 166 ($M^+ - CH_3$, 32), 112 ($M^+ - C_5H_9$, 100), 84 (13), 56 (13), 55 (25), 44 (21), 42 (18), and 41 (41).

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.40; H, 12.80; N, 7.79.

Employing a general reductive amination procedure described previously,[6a] a mixture of 1.35 g (13.6 mmol) of the amine **21**, 0.22 g (2.2 mmol) of the aldehyde **32**, 145 mg (2.2 mmol) of $NaB(CN)H_3$, and 1.8 ml of an aqueous MeOH solution containing 4.4 mmol of HCl was stirred at 25 °C for 5 days. After the resulting mixture had been concentrated and partitioned between Et_2O and aqueous NaOH, the ethereal layer was dried and concentrated to leave 190 mg of crude liquid product containing (GLC, KOH and Carbowax 20M on Chromosorb P) the amine **36**. The amine **36** was collected as 71 mg (18%) of colorless liquid, n^{25}D 1.4638, that was identified with the previously described sample by comparison of ir and NMR spectra and GLC retention times.

Preparation of the Oxime 9. Reaction of 22.4 (0.20 mol) of the aldehyde 8[25] with 20.8 g (0.30 mol) of $HONH_3Cl$ and 14.9 g (0.14 mol) of Na_2CO_3 in 150 ml of H_2O at 0–5 °C for 1 h and at 25 °C for 2 h yielded 21 g (83%) of the oxime **9** as a colorless liquid: bp 64–65 °C (2 mm), n^{25}D 1.4589 [lit.[26] bp 85 °C (17 mm), n^{25}D 1.4565]; ir (CCl_4) 3580, 3300 (OH), and 1640 cm^{-1} (C=N); NMR (CCl_4) δ 8.57 (1 H, s, OH, exchanged with D_2O), 7.27 (1 H, s, CH=N), 4.8–6.1 (3 H, m, vinyl CH), 2.18 (2 H, d, J = 7 Hz, allylic CH_2), and 1.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 127 (M^+, 2), 112 (3), 86 (40), 55 (25), 42 (20), 41 (100), and 39 (45).

Preparation and Cyclization of the Hydroxylamine 7. Reduction of 592 mg (4.65 mmol) of the oxime **9** with 300 mg (4.76 mmol) of $NaB(CN)H_3$ in 5 ml of MeOH (containing methyl orange) for 1 h with the periodic addition of 6 M HCl in H_2O–MeOH yielded the crude hydroxylamine **7**. From a comparable reaction, performed in CH_3OD solution, the NMR of the reaction mixture (in CH_3OD) at this stage exhibited the following peaks attributable to the solvent and the hydroxylamine **7**: δ 4.8–6.3 (m, vinyl CH, OH, and/or NH), 3.85 (s, CH_3O of solvent), 3.17 (s, CH_2N), 2.12 (d, J = 7 Hz, allylic CH_2), and 1.08 (s, CH_3). The reaction mixture was concentrated in a water bath (50–70 °C) under reduced pressure and the residual mixture was made basic with aqueous NaOH, saturated with NaCl, and extracted with Et_2O. After the Et_2O extract had been dried and concentrated, a solution of the residual yellow liquid (the crude hydroxylamine **10**, NMR analysis) in 4.0 ml of pyridine was treated with 2.0 ml of PhCOCl and allowed to stand for 30 min. Then the reaction mixture was partitioned between Et_2O and aqueous 3 M HCl and the Et_2O phase was washed with aqueous $NaHCO_3$, dried, and concentrated. The residual crude product (2.75 g) was chromatographed on silica gel to separate a mixture of $(PhCO)_2O$ and $PhCO_2H$ in early fractions eluted with PhH. The subsequent fractions, eluted with PhH, were washed with aqueous $NaHCO_3$, dried, and concentrated to leave 878 mg of the crude benzoate **11** as a yellow liquid, n^{25}D 1.5096. This material was partially purified by preparative TLC (silica gel coating with a PhH–Et_2O eluent, 1:10 v/v) to separate 691 mg of the benzoate **11** as a yellow liquid, n^{25}D 1.5079. Distillation under reduced pressure in a short-path still afforded 645 mg (60%) of the benzoate **11** as a yellow liquid: n^{25}D 1.5080; ir (CCl_4), 1742 cm^{-1} (C=O); uv max (95% EtOH) 225 nm (ε 14 200), 273 (860), and 280 (710); NMR (CCl_4) δ 7.1–8.1 (5 H, m, aryl CH), 2.0–3.7 (2 H, m, CHN and part of AB system for CH_2N), 2.67 (1 H, d, J = 9.5 Hz, part of AB system for CH_2N), 1.0–2.5 (11 H, m, CH_2 with CH_3 singlets at 1.15 and 1.22 and a CH_3 doublet, J = 7 Hz, at 1.20); mass spectrum *m/e* (rel intensity) 122 (26), 105 (40), 96 (21), 77 (38), 69 (24), 55 (100), 51 (27), and 41 (32). Our efforts to obtain an analytically pure sample of this benzoate **11** were thwarted by the partial decomposition that occurred during each attempt to distill the material.

Reduction of 6.35 g (50 mmol) of the oxime **9** with 3.46 g (55 mmol) of $NaB(CN)H_3$ in 50 ml of MeOH with added methyl orange and 6 M HCl in MeOH–H_2O, followed by concentration of the crude basic product on a steam bath under reduced pressure, left 6.2 g (96%) of the crude liquid hydroxylamine **10**. Reduction of this crude product with 13.1 g (0.20 g-atom) of Zn, 25.5 g (0.25 mol) of Ac_2O, and 24 g (0.40 mol) of HOAc at 80–90 °C for 2 h yielded a crude neutral product. Fractional distillation separated 386 mg of a fraction, bp 70–71 °C (1 mm), n^{25}D 1.4570, containing (GLC, Carbowax 20M on Chromosorb P) ca. 95% of the amide **12** and 3.55 g (total yield 3.93 g or 51%) of the pure amide **12** as a colorless liquid: bp 72–75 °C (1 mm); n^{25}D 1.4580; ir (CCl_4) 1640 cm^{-1} (amide C=O); NMR (CCl_4) δ 2.8–4.3 (3 H, m, CH_2N and CHN) and 0.8–2.2 [14 H, m, aliphatic CH including a CH_3CO singlet at 1.90, a CH_3 doublet (J = 6 Hz) at 1.25, and two CH_3 singlets at 1.12 and 1.01]; mass spectrum *m/e* (rel intensity) 155 (M^+, 20), 140 (20), 99 (22), 98 (100), 57 (70), 56 (26), 55 (18), 43 (52), 42 (18), and 41 (25).

Anal. Calcd for $C_9H_{17}NO$: C, 67.63; H. 11.04; N, 9.02. Found: C, 69.67; H, 11.07; N, 9.07.

Preparation of the Hydroxylamine 38. Following a previously described[16] procedure with 20.32 g (0.20 mol) of the aldehyde **40**, 20.85 g (0.30 mol) of $HONH_3Cl$, 14.8 g (0.14 mol) of Na_2CO_3, and 50 ml of H_2O, the oxime **41** was obtained as 20.55 g (82%) of colorless liquid: bp 80–82 °C (1.5 mm), n^{25}D 1.5065 [lit.[16] bp 106–107 °C (10 mm), n^{20}D 1.5040]; ir (CCl_4) 3570, 3300 (OH), and 1645 cm^{-1} (C=N and C=C); NMR (CCl_4) δ 9.25 (1 H, broad, OH), two doublets at 7.32 (J = 6 Hz) and 6.58 (J = 7 Hz) (total 1 H, CH=N of syn and anti isomers), 5.4–5.8 (2 H, m, vinyl CH), and 1.3–3.5 (7 H, m aliphatic CH); mass spectrum *m/e* (rel intensity) 125 (M^+, 16), 108 (20), 93 (64), 91 (40), 81 (31), 80 (100), 79 (69), 77 (32), 67 (35), 54 (76), 53 (32), 41 (53), and 39 (62). Reduction of 1.25 g (10 mmol) of the oxime **41** with 755 mg (12 mmol) of $NaB(CN)H_3$ in 10 ml of MeOH with added methyl orange and 6 M HCl in H_2O–MeOH for 1 h gave 1.28 g of the crude hydroxylamine **38** as a pale yellow liquid: NMR (CCl_4) δ 6.22 (2 H, broad, NH and OH), 5.4–5.7 (2 H, m, vinyl CH), 1.3–3.0 (9 H, m, aliphatic CH). After a sample of this hydroxylamine **38** had been heated to 170 °C for 1 h, NMR analysis of the crude product indicated that the vinyl CH absorption was undiminished and, consequently, cyclization had not occurred. A solution of 1.09 g of the crude hydroxylamine **38** and 4 ml of PhCOCl in 6 ml of pyridine was stirred for 30 min and then partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried and concentrated and the residue (4.2 g) was chromatographed on silica gel with PhH–hexane mixtures as eluents. After separation of early fractions containing $(PhCO)_2O$, subsequent fractions contained 2.61 g of the crude dibenzoyl compound **42** as a yellow liquid, ir (CCl_4), 1765 (ester C=O) and 1680 cm^{-1} (amide C=O). A solution of 1.75 g of this dibenzoyl compound **42** and 4 g of KOH in 10 ml of MeOH was stirred at 25 °C for 24 h and then acidified, concentrated, and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual yellow solid (868 mg, mp 105–109 °C) was recrystallized from a $CHCl_3$–hexane mixture to separate 663 mg (43%) of the hydroxamic acid **43** as colorless needles: mp 112–113 °C; ir (CCl_4) 3220 (OH) and 1610 cm^{-1} (amide C=O); NMR (CCl_4) δ 7.3–7.7 (5 H, m, aryl CH), 5.5–5.7 (2 H, m, vinyl CH), 3.58 (2 H, d, J = 6.5 Hz, CH_2N), and 1.0–2.5 (8 H, m, OH and aliphatic CH); uv max (95% EtOH) 235 nm (broad, ε 4600); mass spectrum *m/e* (rel intensity) 231 (M^+, 1), 213 (5), 150 (6), 105 (100), 94 (7), 77 (41), 41 (9), and 39 (7).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.65; H, 7.42; N, 6.02.

Preparation of the Oxime 46. Following a previously described procedure,[27] a THF solution of $(CH_3)_2C$=$CHCH_2MgCl$ was carbonated with crushed dry ice to yield 74% of the acid **44** as colorless liquid: bp 101–102 °C (26 mm), n^{25}D 1.4280 [lit. bp 100–102 °C (28 mm),[27] n^{25}D 1.4272,[28] 1.4295[27]]; ir (CCl_4) 3000 (broad, carboxyl OH), 1695 (C=O), 1637 (C=C), and 925 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 12.15 (1 H, s, OH), 4.8–6.3 (3 H, m, CH=CH_2), and 1.28 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 114 (M^+, 3), 99 (14), 69 (72), 41 (100), and 39 (20). Although the same acid **44** was obtained by the previously described[28] carbonation of $(CH_3)_2C$=$CHCH_2MgBr$, the overall yield (36%) was lower. To a cold (−40 to −60 °C) solution of 22.8 g (200 mmol) of the acid **44** in 100 ml of Et_2O was added, dropwise and with stirring and cooling, 500 ml of an Et_2O solution containing 0.46 mol of MeLi.[29] After approximately 1 equiv of the MeLi solution had been added and the vigorous evolution of CH_4 subsided, the mixture was warmed and maintained at −10 °C while the second equivalent of MeLi was added. Use of this procedure diminished the amount of alcohol **47** by-product that was formed. After the resulting suspension had been stirred at 25 °C for 2 h, it was added, slowly with vigorous stirring, to dilute aqueous HCl and then extracted with Et_2O. The ethereal extract was washed with aqueous NaOH, dried, and fractionally distilled to separate 16.6 g (74%) of the pure (GLC) ketone

45, bp 52–55 °C (55 mm), n^{25}D 1.4221 (lit.[30] bp 129.5 °C), and 1.3 g (6%) of a fraction, bp 56–58 °C (55 mm), n^{25}D 1.4230, that contained (GLC, Carbowax 20M on Chromosorb P) the desired ketone 45 (ca. 95%, retention time 4.4 min) accompanied by the alcohol 47 (ca. 5%, 6.8 min). The spectral properties of the ketone 45 were: ir (CCl_4) 1710 (C=O), 1635 (C=C), and 935 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.2 (3 H, m, CH=CH_2), 2.01 (3 H, s, $COCH_3$), and 1.20 (6 H, s, CH_3). Reaction of 15.0 g (134 mmol) of the ketone 45 with 14.0 g (200 mmol) of $HONH_3Cl$ and 10.0 g (94 mmol) of Na_2CO_3 in 150 ml of H_2O for 1 h at 0 °C and for 1 h at 25 °C yielded 7.44 g (43%) of the oxime 46 as a colorless liquid: bp 57–58 °C (1 mm), n^{25}D 1.4670; ir (CCl_4) 3580, 3250 (OH), 1635 (C=N), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 9.45 (1 H, broad, OH), 4.8–6.2 (3 H, m, CH=CH_2), 1.75 (3 H, s, CH_3C=N), and 1.20 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 112 (24), 69 (34), 68 (14), 67 (18), 42 (25), 41 (100), 40 (33), and 39 (29).

Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.15; H, 10.30; N, 11.00.

Preparation of the Hydroxylamine 39. Reduction of 508 mg (4.0 mmol) of the oxime 46 with 234 mg (45 mmol) of $NaB(CN)H_3$ in 20 ml of MeOH at pH 3–4, following previously described reaction and isolation procedures, yielded the crude liquid hydroxylamine 39: NMR (CCl_4) δ 4.7–6.1 (5 H, m, CH=CH_2, OH, and NH), 2.75 (1 H, q, J = 6.5 Hz, CHN), 1.08 (3 H, partially resolved d, J = 6.5 Hz, CH_3) and two partially resolved CH_3 singlets (total 6 H) at 1.00 and 0.97. This crude hydroxylamine 39 was mixed with 1.0 g (12.7 mmol) of pyridine and 2.0 g (14.2 mmol) of PhCOCl and allowed to stand for 10 min. After the resulting mixture had been stirred with 10 ml of aqueous 6 M KOH for 3 min, it was extracted with Et_2O and the ethereal extract was dried and concentrated to leave a residual liquid containing (ir analysis) a mixture of $(PhCO)_2O$ and the dibenzoyl derivative 50. A solution of this crude product and 4.0 g of NaOH in 20 ml of MeOH was heated on a steam bath for 5 min and then diluted with H_2O, concentrated to remove the MeOH, acidified, and extracted with Et_2O. After the ethereal extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residue was crystallized from cold hexane to separate 615 mg (66% from the oxime 46) of the hydroxamic acid 51 as pale yellow needles, mp 72–75 °C. Recrystallization afforded 470 mg (51%) of the pure hydroxamic acid 51 as colorless needles: mp 76–77 °; ir (CCl_4) 1640 (shoulder, C=C), 1615 (hydroxamic acid C=O), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 8.33 (1 H, broad, OH, exchanged with D_2O), 7.2–7.6 (5 H, m, aryl CH), 4.7–6.2 (3 H, m, CH=CH_2), 3.88 (1 H, q, J = 7 Hz, CHN), 1.25 (3 H, d, J = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), and 1.03 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity), 164 (4), 148 (12), 105 (100), 77 (36), 51 (13), 42 (14), and 41 (23); uv (95% EtOH) end absorption (ε 7910 at 210 nm) with shoulders at 219 nm (ε 6940) and 240 (5520).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.04; H, 8.22; N, 5.95.

A solution of the crude hydroxylamine 39 (uncontaminated with the oxime 46, NMR analysis), from 2.54 g (20 mmol) of the oxime 46 and 1.57 g (25 mmol) of $NaB(CN)H_3$, in 25 ml of $PhCH_3$ was added through a high-dilution head[17] to 50 ml of refluxing $PhCH_3$ during 40 min. After the resulting solution had been refluxed for an additional 1 h, it was concentrated to leave a residual liquid with NMR absorption corresponding to the starting material 39. After a solution of the crude hydroxylamine 39 in xylene had been refluxed for 4 h and concentrated, the residual liquid contained (NMR analysis) a mixture of the starting hydroxylamine 39 and the oxime 46 formed by oxidation of the hydroxylamine 39 during the heating process.

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References and Notes

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Studies on the Formation of Dyes Derived from Diindolylpyridylmethanes

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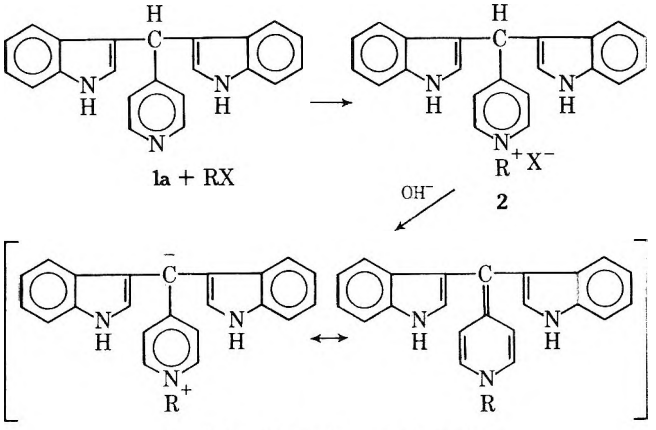
Diindolylpyridylmethane derivatives **1a–l** (except **1k**) upon N-alkylation of the pyridine moiety and treatment with base produce dyes analogous to **3**. Unexpectedly, dye production from **2** was accompanied by rapid autoxidation to yield dye **4** followed by slow dealkylation to dye **5**. Dye **5** was also obtained by Pd/C dehydrogenation of **1a** and alternatively by nitric acid oxidation of **1a**. The corresponding 1-methyldiindolyl **1e** and 1,1′-dimethyldiindolyl **1c** derivatives gave dyes analogous to **3** but not to **4**. The 3-pyridyl derivative **1m** did not form dyes. The kinetics of methylation of seven diindolylpyridylmethane derivatives with methyl iodide in 1:1 (v/v) 2-methoxyethanol–acetonitrile solvent mixture were determined at 30 °C spectrophotometrically and it was found that substituents in the indolyl moiety had little effect on the rate. The second-order rate constants varied between 5.2 and 6.0 $\times 10^{-4}$ l. mol^{-1} s^{-1}. Second-order rate constants for methylation of eight 3- and 4-substituted pyridines with methyl iodide in methanol-d_4 were determined at 30 °C by NMR and were found to range from 0.2 to 5.6 $\times 10^{-5}$ l. mol^{-1} s^{-1}.

While 4-(4-nitrobenzyl)pyridine has been extensively employed for the assay and detection of alkylating agents in the microgram range[1–3], under certain conditions the reagent for unknown reasons displays an unacceptable blank in alkali. Also the rate of alkylation of 4-(4-nitrobenzyl)pyridine is relatively slow at ambient temperatures. Therefore a search was made for reagents that would obviate these disadvantages.

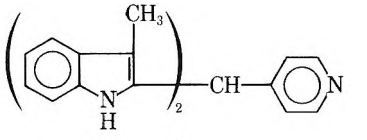
Diindolylpyridylmethane (**1a**) (Scheme I) was expected to yield a colored alkylation product **3** in basic solution. Unexpectedly, **3** has been found to undergo a rapid oxidation followed by a slower dealkylation.

Scheme I

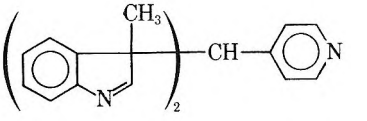


3

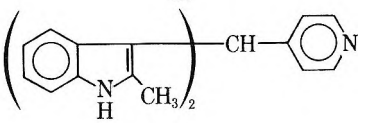
The diindolylpyridylmethanes (Table I) were prepared by condensation of an indole (2 equiv) and 4-pyridinecarboxaldehyde (1 equiv) in ethanolic hydrochloric acid, a method found superior to published procedures.[4,5] All compounds were 3,3′-diindolylpyridylmethanes except for **1k** which resulted from electrophilic attack at the 2 position of skatole. NMR data excluded **1k′** (indole N–H resonances, broad singlet δ 10.45). Compound **1k** differed from **1c** obtained by condensation of 2-methylindole with 4-pyridinecarboxaldehyde. Condensation of formaldehyde and benzaldehyde with skatole reportedly occurred at the 2 position.[6] Unsymmetrical **1e** (accompanied by **1a** and **1b**) was prepared in low yield from equimolar quantities of indole, 1-methylindole, and 4-pyridinecarboxaldehyde. NMR and



1k

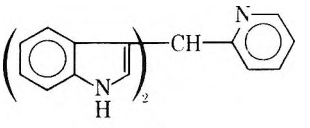


1k′

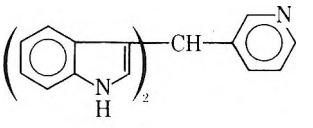


1c

mass spectral data were consistent with the proposed structure. An attempt to isolate the expected carbinol intermediate[5] failed. Use of 2- and 3-pyridinecarboxaldehyde afforded **1l** and **1m**.



1l



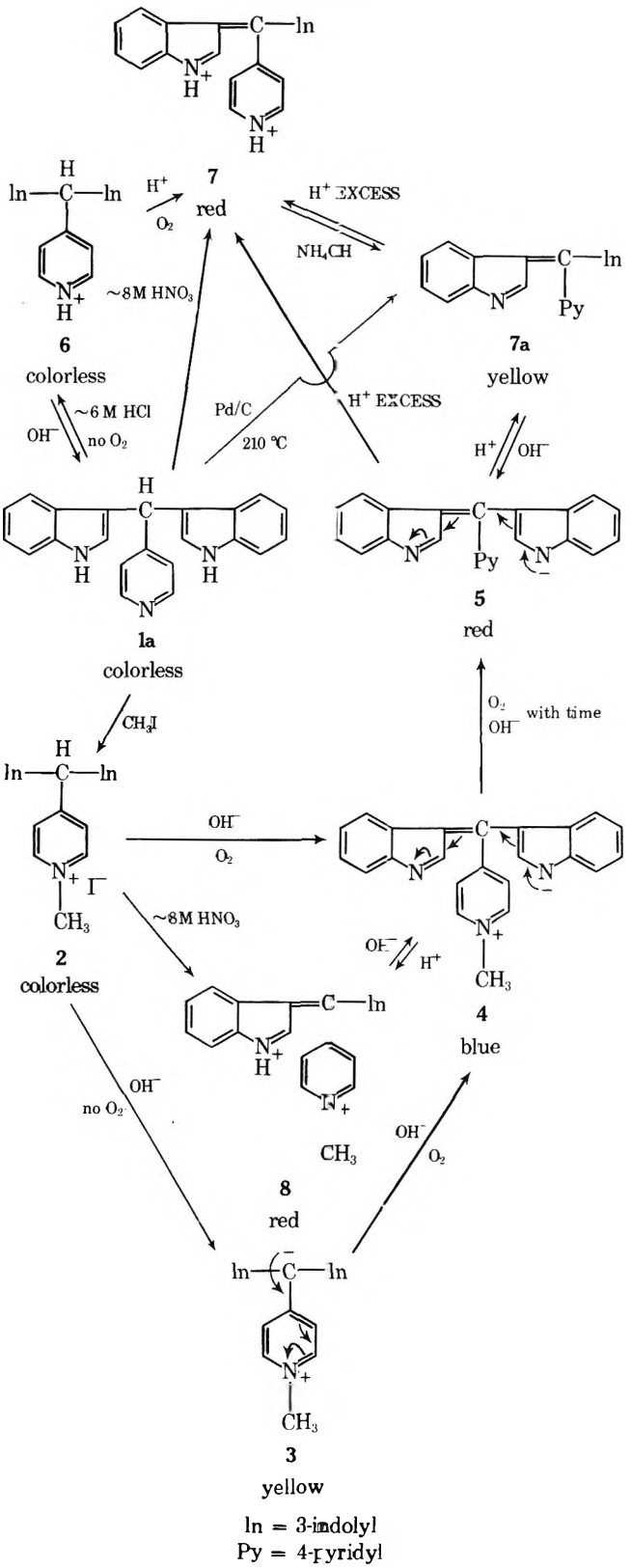
1m

Alkylation of **1a** with methyl iodide gave principally the *N*-methyl pyridinium salt showing poor analytical data. NMR spectra showed an impurity(δ 3.2, Me_2SO-d_6). Analytically pure *N*-methyl salt was prepared from 4-pyridinecarboxaldehyde methiodide and indole in ethanolic hydrogen iodide. The δ 3.2 resonance was greatly reduced. A number of experiments were carried out to probe the structures of the various dyes. Scheme II summarizes these experiments and the structures presented appear to be the only reasonable ones consistent with the following data.

Treatment of **1a** with excess methyl iodide produced colorless **2**. Compound **1a** with excess methyl iodide and base in the presence of oxygen produced a blue dye, **4** (λ_{max} 575 nm, ϵ 1.4 $\times 10^4$). Compound **2** with base under argon gave a yellow dye, **3**, which immediately turned blue upon exposure to oxygen.

In support of the proposed structures of **3** and **4**, alkylation of di(1-methylindolyl)-4-pyridylmethane (**1b**) followed

Scheme II



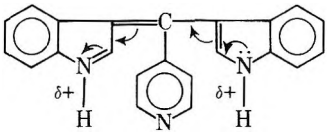
by treatment with base in the presence of oxygen did not form a blue dye. This carbanion is incapable of oxidation to the rosindole chromophore because it lacks the indole NH.

The unsymmetrical **1e** with one indole nitrogen substituted by a methyl group underwent alkylation with excess methyl iodide to produce a colorless product that became red when treated with alkali. This compound can give a carbanion that is oxidized to a rosindole (λ_{max} 543 nm, ϵ 1.6 $\times$ 10^3), but does not have the second indole NH needed to produce blue dye **4**. These experiments showed that one indole NH is necessary for oxidation and two are necessary for the blue dye **4**.[7a]

Compound **2** with 8 M HNO_3 under argon produced a red dye, **8** (λ_{max} 547 nm, ϵ 2.1 $\times$ 10^4), which gave **4** on treatment with deoxygenated base. Compound **4** was converted to **8** on treatment with 8 M HNO_3. Treatment of **1a** with 8 M HNO_3 also produced a red dye, **7** (λ_{max} 543 nm, ϵ 2.0 $\times$ 10^4) whose spectral properties were nearly identical with those of **8** (λ_{max} 547 nm, ϵ 2.1 $\times$ 10^4).

In support of structure **7**, **1a** in 6 M HCl gave a colorless solution, which became red (**7**) upon exposure to oxygen for several days. Compound **7** was not converted to **1a** by base. This established that **7** was an oxidation product of **1a**. Compound **7** (λ_{max} 540 nm, ϵ 2.6 $\times$ 10^4) was likewise produced by refluxing **1a** in nitrobenzene in the presence of 5% Pd/C catalyst,[7b] isolation of the free base **7a**, and dissolution in hydrochloric acid. Compound **7** obtained from **1a** by treatment with 8 M HNO_3 was converted to **7a** with ammonium hydroxide. While a satisfactory elemental analysis was not obtained, the mass spectrum of **7a** showed a parent peak *m/e* 321 (rel intensity 1.0), P − 1 (rel intensity 0.6). The loss of a hydrogen atom from the parent cation would lead to a resonance-stabilized radical cation.

Compound **7a** was converted to a dihydrochloride, **7**, whose NMR showed a sharp two-proton resonance for the α-indole and indolinenyl protons (δ 8.6) and no triarylmethinyl proton. This established the structure of **7**. The monoprotonated form of **7a** showed λ_{max} 512 nm. The



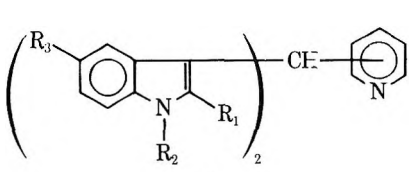
monoprotonated form of **7a**

NMR of **7a** (Me_2SO-d_6–D_2O) showed no triarylmethinyl proton and two equivalent α-indolyl protons (δ 8.0) shifted upfield from **7**, as expected. The absence of α-indolyl and indolinenyl proton resonances was due to rapid deuteron exchange with solvent. These observations were in accord with **7** and **7a**. Treatment of **7a** (λ_{max} 450 nm, ϵ 2.6 $\times$ 10^4) with excess methanolic sodium hydroxide yielded **5** (λ_{max} 521 nm, ϵ 3.6 $\times$ 10^4). Thus, **7a** contained an acidic proton (a conjugated indole NH), two basic sites (pyridyl N and indolinenyl N), and no triarylmethinyl proton and had molecular weight 321 (mass spectrum). Coupled with the fact that **7a** was obtained by oxidation or catalytic dehydrogenation, these data firmly established the structures of **7a** and **5**.

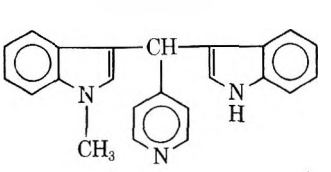
TLC analysis of a preparative scale solution of **5** on silica gel gave a compound whose R_f value was identical with that of **7a**. These data indicate the loss of an *N*-methyl group in the conversion of **4** to **5**. Compound **2** was treated preparatively with potassium hydroxide in methanol to produce **5**. The product was isolated by evaporation and extraction with benzene. TLC analysis of the solid recovered from an aliquot of the benzene solution indicated one component (R_f 0.5, **7a**) and a minor contaminant (R_f 0.7). A portion of the benzene solution was evaporated on the probe of the mass spectrometer. The mass spectrum showed a major *m/e* 321 and an unexplained weaker peak *m/e* 323. The latter *m/e* cannot be ascribed to **1a** because the characteristic blue color was not obtained upon treatment with dimethyl sulfate and base.[8]

A portion of the benzene solution of **7a** obtained from **4** was extracted with aqueous hydrochloric acid and the extract was evaporated to dryness. The NMR in methanol-d_4 showed the characteristic A_2B_2 pattern of a 4-substituted

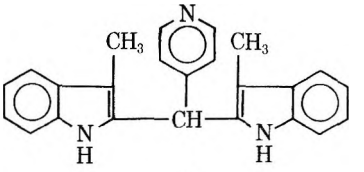
Table I. Diindolylpyridylmethanes[a]



1



1e



1k

Compd	Ar	R_1	R_2	R_3	Mp, °C	Elemental anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1a	4-Pyridyl[c]	H	H	H	156–158 dec	81.7	5.3	13.0	81.9	5.5	13.0
1b	4-Pyridyl[d]	H	CH_3	H	184–185 dec	82.0	6.0	12.0	81.7	6.3	11.7
1c	4-Pyridyl[e]	CH_3	H	H	241–244 dec	78.0	6.3	11.4	78.0	6.0	11.5
1d	4-Pyridyl	H	H	CH_3	256–260 dec	82.0	6.0	12.0	81.7	5.9	12.0
1e[b]					146–148 dec	81.9	5.7	12.4	80.1	5.7	12.0
1f	4-Pyridyl	H	H	Cl	231–263 dec	67.4	3.9	10.7	67.1	4.0	10.5
1g[b]	4-Pyridyl	H	H	Br	275–277 dec	54.9	3.1	8.7	55.2	3.3	9.4
1h	4-Pyridyl	H	H	CN	274–276 dec	77.2	4.0	18.8	77.0	4.2	18.8
1i	4-Pyridyl	H	H	COOH	185–188 dec	70.1	4.2	10.2	69.0	4.3	10.3
1j[b]	4-Pyridyl	H	H	CH_3O	181–185 dec	75.2	5.5	11.0	74.6	5.6	10.9
1k					264–266 dec	82.0	6.0	12.0	81.9	6.2	12.2
1l	2-Pyridyl	H	H	H	212 dec	81.7	5.3	13.0	81.9	5.3	13.1
1m	3-Pyridyl	H	H	H	102–107 dec	81.7	5.3	13.0	83.1	5.7	10.7

[a] Substantial parent peaks were shown by these compounds. [b] Analyses unsatisfactory; homogeneous by TLC under conditions that separate 1a and 1b. [c] Lit. mp 152–155°C dec (ref 4) and 155–156°C dec (ref 5). [d] Lit. mp 186–188°C dec (ref 4). [e] Lit. mp 249–250°C uncorrected (ref 13).

Table II. Second-Order Rate Constants for the Reaction of Diindolylpyridylmethanes and 4-(4-Nitrobenzyl)pyridine with Methyl Iodide at 30°C[a]

Compd	Substituent	$k_2 \times 10^4$, l. mol^{-1} s^{-1}	λ_{max}, nm	$\epsilon \times 10^{-4}$, M^{-1} cm^{-1} Calcd	Corrected
1a	H	5.9	575[b]	1.4	1.4
1c	2-CH_3	5.9	644[b]	1.0	1.1
1d	5-CH_3	5.9	578[b]	1.2	1.3
1f	5-Cl	5.2	556[b]	1.3	1.3
1g	5-Br	5.7	559[b]	1.1	1.3
1h	5-CN	6.0	532[c]	1.4	1.4
1j	5-CH_3O	5.9	562[b]	1.1	1.3
4-(4-Nitrobenzyl)pyridine[e]		4.5	559[d]	2.5	2.5

[a] Second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the methyl iodide concentration. [b] For compound 4. [c] For compound 5. [d] For the dye.[3] [e] Registry no., 1083-40-3.

pyridine, the equivalent α hydrogens of indole, the eight benzenoid protons, and no triarylmethinyl proton. Significantly, the *N*-methyl resonance was present as only a minor feature (<10 mol %) of the spectrum. This spectrum had the significant features of the rosindole **7** prepared via the catalytic route except for an unexplained resonance at δ 7.5, assigned to an impurity. All the evidence points to a loss of an *N*-methyl group in the conversion of **4** to **5**. While nucleophilic displacement on the pyridinium *N*-methyl group was not anticipated, there is ample evidence for carbanion formation at this site;[9,10] and thus, a likely pathway is the oxidative cleavage of the methyl–nitrogen bond via a carbanion as suggested by Corwin et al. for viologen dealkylation.[11] When compound **9**, the *N*-benzyl chloride analogue of **2**, was treated with base, benzaldehyde was detected by GLC analysis. Alkylation of **7a** was attempted with excess dimethyl sulfate followed by addition of base. This procedure, however, did not produce the characteristic blue color of **4**. The most likely side reaction to account for this failure was the alkylation of the indolenine nitrogen, the most basic site in **5**.[12]

The presence of the pyridinium moiety in the rosindole has a marked effect on the rosindole chromophore. The rosindole **7a** in alkali has λ_{max} 521 nm (ϵ 3.6 × 10^4) while **4** has λ_{max} 575 nm (ϵ 1.4 × 10^4). This bathochromic shift seems unusually large for a substituent in a cross conjugated position.

In the 2-pyridyl series, the independently prepared *N*-methylpyridinium compound on treatment with alkali and oxygen gave a dye with λ_{max} 550 nm (ϵ 2.8 × 10^4). Qualitatively, the 2-pyridyl compound **1l** underwent alkylation much more slowly than **1a**. The corresponding 3-pyridyl compound gave a colorless solution in base suggesting that neither a carbanion nor a rosindole was formed. Evidently conjugation of the triarylmethyl carbanion center with the pyridinium nitrogen is necessary for ready carbanion formation and carbanion formation is a prerequisite for facile oxidation to rosindole. The λ_{max} of the dye resulting from treatment of the 2-pyridinium compound with base was 25 nm hypsochromically shifted compared to the 4-pyridinium compound. The structure of the 2-pyridinium dye would be expected to deviate from coplanarity more than that of the 4-pyridinium dye.

All of the di(5-substituted indolyl)-4-pyridylmethane compounds **1d–g** (Table I) gave dyes upon alkylation and subsequent treatment with base. The spectral characteristics are given in Table II.

The N-methylated 5-cyano derivative (**1h**) formed a blue dye in base that was rapidly converted to the red dye (λ_{max} 532 nm, ϵ 2.8 × 10^4) presumably corresponding to the deal-

Table III. Second-Order Rate Constants for the Reaction of 3- and 4-Substituted Pyridines with Methyl Iodide at 30°C[a]

Substituent	H	4-CH_3	4-CN	3-CN	4-CH_2OH	3-CH_2OH	4-C_6H_5	3-$CONH_2$
$k_2 \times 10^5$, l. mol^{-1} s^{-1}	4.0	5.5	0.4	0.2	2.8	5.6	4.7	1.7
Registry no.	110-86-1	108-89-4	100-48-1	100-54-9	586-95-8	100-55-0	939-23-1	98-92-0

[a] Obtained by NMR.

kylated product **5**. The conversion of the blue dye from the methiodide of **1h** to the red dye was complete in 5 min while the conversion of **4** to **5** required ca. 8 h under the same conditions.

Kinetics of Alkylation of Substituted Pyridines. Kinetic studies were carried out on the rates of methylation with excess methyl iodide of the substituted diindolylpyridylmethanes. The reactions were carried out at 30 °C in a 1:1 (v/v) 2-methoxyethanol–acetonitrile solvent mixture with a 1000-fold excess of methyl iodide. An aliquot of the reaction mixture was withdrawn periodically, diluted with aqueous base, and the absorbance read at the appropriate λ_{max} (Table II). The reaction was followed for 2–3 half-lives. After approximately 15 h, the absorbance of an aliquot was read and the molar absorptivity was calculated assuming complete reaction. The molar absorptivities are recorded in Table II. The use of the 15-h absorbance as the infinity value for the kinetic calculations resulted in poor pseudo-first-order plots. By trial and error a molar absorptivity value was chosen to give a straight-line first-order plot. The corrected molar absorptivities are shown in the last column of Table II. The second-order rate constants were calculated using the corrected molar absorptivities. The rate constants were found to be insensitive to substituents in the indole ring (Table I).

For comparison, rates of alkylation of various pyridine compounds were determined by NMR (Table III) by measurement of the rates of appearance of the *N*-methyl resonance and disappearance of the methyl iodide resonance. The reactions were carried out using equimolar concentrations of reactants.

The data in Table III show that substituents introduced directly into the pyridine ring show less than a 30-fold variation in the rate of alkylation, so it is not surprising that rates of alkylation of compounds **1a–j** are relatively insensitive to substitution in the indole nucleus.

Quantitative comparison of the data in Table II and III is not possible owing to solvent difference.

Experimental Section

Melting points are corrected. Elemental analyses were performed by the Chemical Laboratory, Edgewood Arsenal. Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer. Electronic spectra were obtained on a Cary 14 spectrophotometer. The NMR spectra were measured with a Varian A-60D instrument using Me_2SO-d_6, acetone-d_6, or methanol-d_4 and Me_4Si as the internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6E at 70 eV. For gas chromatography a Hewlett-Packard 5750 instrument was used. Unless otherwise noted thin layer chromatography (TLC) was performed on Eastman silica gel chromatogram sheets containing a fluorescent indicator. Compounds were visualized with 254-nm light. Molar absorptivities are given in M^{-1} cm^{-1} units.

Melting points and analytical data for the diindolylpyridylmethanes are given in Table I.

3,3′-Diindolyl-4-pyridylmethane (1a) was prepared by dissolving indole (2.34 g, 0.02 mol) and 4-pyridinecarboxaldehyde (1.07 g, 0.01 mol) in ethanol (100 ml). Acid (20 ml of concentrated HCl) was added and the solvent was allowed to stand at 25 °C for 2 h. Water (300 ml) was added giving a fine white precipitate. The milky suspension was neutralized with concentrated NH_4OH, yielding a yellow precipitate. After filtration and drying, 2.87 g (89% yield) of **1a** was obtained. The solid was recrystallized from methanol to obtain white prisms. After a tenfold dilution of a methanolic solution of **1a** with 1:1 (v/v) concentrated HCl–H_2O no color was visible. However, the solution slowly turned red. After 198 min the spectrum was obtained: λ_{max} 545 nm (ϵ 8×10^1) (**1a** → **6** → **7** incomplete reaction). After diluting a methanolic solution of **1a** tenfold with 1:1 (v/v) concentrated HNO_3–H_2O a red solution was obtained, λ_{max} 543 nm (ϵ 2.0×10^4) (**1a** → **7**).

3,3′-Di(5-cyanoindolyl)-4-pyridylmethane (1h) was prepared from 5-cyanoindole (2.84 g, 0.02 mol) and 4-pyridinecarboxaldehyde (1.07 g, 0.01 mol) in ethanol (150 ml) with 30 ml of concentrated HCl. After 1 week at 25 °C, water (300 ml) was added and the solution was neutralized with NH_4OH. The mixture was cooled and the white crystals of **1h** were filtered and dried (2.29 g, 61.4% yield). The solid recrystallized from methanol.

The other symmetrical compounds in Table I, **1b, 1c, 1d, 1f, 1g, 1i, 1j, 1k, 1l,** and **1m,** were prepared similarly with reaction times varying from 2 h to 1 week with yields varying from 40 to 60%. Satisfactory analyses were generally obtained by slow recrystallization overnight from methanol at 25 °C.[13]

3,3′-Di(5-carboxyindolyl)-4-pyridylmethane (1i) was prepared on one-tenth the scale used for **1a.** A mixture of five products resulted (TLC, hexane–ethyl ether–ethanol, 5:5:2). The crude product was chromatographed on neutral alumina (Woelm activity I) eluting with acetonitrile until all the impurities were removed (TLC). The product **1i** was eluted with methanol.

3-Indolyl-3′-(1-methylindolyl)-4-pyridylmethane (1e) was prepared by allowing indole (1.17 g, 0.01 mol), 1-methylindole (1.31 g, 0.01 mol), and 4-pyridinecarboxaldehyde (1.07 g, 0.01 mol) to react in ethanol (100 ml) containing concentrated HCl (20 ml) at 25 °C for 2 h. Water (300 ml) was added and the mixture was neutralized with NH_4OH. The precipitate was filtered, dried, and chromatographed on basic alumina (Woelm activity I), eluting with dichloromethane.

3,3′-Diindolyl-4-pyridylmethane Methiodide (2). Method A. Compound **1a** (1 g) was dissolved in acetone (20 ml) containing methyl iodide (20 ml). After 1 h the yellow crystals were filtered and dried, giving 0.35 g (24% yield) of **2.** The solid recrystallized from methanol gave an unsatisfactory elemental analysis. The purity of **2** was monitored by measuring the molar absorptivity of **4** at 575 nm by dissolving **2** in a 1:1 (v/v) mixture of 2-methoxyethanol and acetonitrile, diluting to 10^{-4} M, and adding an equal volume of 2 N NaOH. The molar absorptivities that were obtained using **2** after successive recrystallizations were 1.43×10^4, 1.43×10^4, and 1.41×10^4, respectively.

Method B. Methyl iodide (15.6 g, 0.11 mol) was added to 4-pyridinecarboxaldehyde (10.7 g, 0.1 mol) in 10 ml of acetonitrile. After refluxing for 15 h, the solution was cooled and poured into acetone (300 ml). The precipitate was collected and dried. A portion of the crude 4-pyridinecarboxaldehyde methiodide (0.01 mol) was dissolved in ethanol (100 ml) containing indole (0.02 mol and concentrated HI (10 ml). After 2 h at 25 °C, 300 ml of water was added. The precipitate was filtered, dried, and recrystallized from methanol, mp 200–208 °C dec (darkens above 116 °C). Anal. Calcd for $C_{25}H_{20}N_3I$: C, 59.4; H, 4.3; N, 9.0; I, 27.3. Found: C, 59.3; H, 4.5; N, 9.1; I, 27.3. The NMR spectral data were in accord with the assigned structure except for an unexplained resonance at δ 3.2. The molar absorptivity obtained for this product **2** after treatment with alkali at 575 nm was 1.43×10^4.

Preparation of the Benzyl Chloride Salt of 1a (9). Compound **9** was prepared by dissolving **1a** (3.23 g, 0.01 mol) and benzyl chloride (1.27 g, 0.01 mol) in benzene (50 ml). After refluxing for 18 h the precipitate was collected and dried to obtain 1.16 g (26% yield) of **9.** The product was recrystallized from water containing sodium chloride, mp 175 °C dec (darkens above 150 °C). Anal. Calcd for $C_{29}H_{24}N_3Cl \cdot H_2O$: C, 74.4; H, 5.6; N, 9.0; Cl, 7.6. Found: C, 74.9; H, 5.5; N, 9.4; Cl, 7.3.

Reaction of 9 with Potassium Hydroxide in Methanol and Gas Chromatography of Products. Compound **9** (1 g) in 1 N methanolic KOH (20 ml) was stirred for 2 h at 25 °C and acidified with 10% HCl. The mixture was evaporated in a stream of air. The semisolid mass was extracted with benzene (20 ml) and the solution was analyzed by GLC (6-ft column containing UCW 98 on 80–100 mesh Chromosorb W at 110 °C). The single peak had the retention time of benzaldehyde.

Preparation of Rosindoles. 3-Indolinylidene-3′-indolyl-4-pyridylmethane (7a). Method A. Compound **1a** (0.5 g) in nitroben-

Table IV. Chemical Shifts of the Pyridinium Methiodides[a]

Pyridine substituent[b]	H	4-CH_3	3-$CONH_2$	3-CN	4-CN	3-CH_2OH	4-CH_2OH	4-C_6H_5
$\overset{+}{N}$–Me resonance, ppm	4.51	4.39	4.55	4.58	4.60	4.48	4.43	4.47
Registry no.	930-73-4	2301-80-6	6456-44-6	1004-16-6	1194-04-3	42330-63-2	43330-64-3	36913-39-0

[a] CH_3I resonance varied between δ 2.16 amd 2.19 depending on the substituted pyridine that was used.

zene (60 ml) was treated with 5% Pd/C catalyst (Engelhard) (0.3 g). The mixture was refluxed under argon for 4 h. TLC (ethyl acetate) of a 1-μl aliquot of the solution showed no starting material. The solution was extracted with 200 ml of 1:4 (v/v) concentrated HCl–H_2O. The acid solution was extracted with one 500-ml and two 300-ml portions of benzene. The aqueous phase was neutralized with NH_4OH. The air-sensitive product was filtered, washed with water, and dried in vacuo for 16 h. The dried solid (7a) weighed 0.37 g, λ_{max} (methanol) 450 nm (ε 1.6 × 10^4). A solution prepared by dissolving **7a** in a stoichiometric amount of HCl (aqueous) showed λ_{max} 512 nm (ε 1.3 × 10^4). A methanolic solution of **7a** diluted tenfold with 1:1 (v/v) concentrated HNO_3–H_2O showed λ_{max} 540 nm (ε 2.6 × 10^4) (**7a** → **7**). The methanolic solution of **7a** diluted tenfold with 2 N NaOH (aqueous) gave λ_{max} 521 nm (ε 3.6 × 10^4) (**7a** → **5**). TLC of **7a** on silica gel (acetone) indicated a major spot, R_f 0.5, with a minor spot, R_f 0.7. The mass spectrum showed a major peak, *m/e* 321 (**7a**), and a weaker peak, *m/e* 323. The compound corresponding to *m/e* 323 was not identical with the starting **1a** (mol wt 323) by TLC or colorimetric analysis. The R_f 0.7 spot on a TLC strip turned purple on exposure to acid vapors and on subsequent treatment with base it became deep red. Similar behavior was observed with the R_f 0.5 spot. Preparative chromatography (2.0 mm silica gel plates) using acetone gave two bands. The lower band was removed and extracted with methanol. Both the R_f 0.5 and the R_f 0.7 spots were evident in a TLC of the extract. Furthermore, the extract contained a relatively larger proportion of the R_f 0.7 material as compared with the sample chromatographed. This result suggests that the two materials were interconverted in the elution process.

Method B. Compound **1a** (1 g) was stirred in 1:1 (v/v) concentrated HNO_3–H_2O. The deep purple solution was neutralized with NH_4OH. The precipitate was filtered and washed with water. TLC on silica gel (acetone) showed spots at R_f 0.5 and 0.7 which showed the same color reactions and mass spectral data as the product from method A.

3-Indolinylidene-3′-indolyl-4-pyridylmethane Dihydrochloride (Dihydrochloride of 7a). The synthesis was the same as that for **7a** (method A) except that the aqueous acid extract was evaporated without neutralization. The recovery of the purple dihydrochloride **7** was 96%. The NMR spectrum in methanol-d_4 showed no triarylmethinyl proton (δ 6.0), but showed a 4-substituted pyridine A_2B_2 quartet: δ 9.25 (2 H, α-pyridine, *J* = 6.0 Hz), 8.42 (2 H, β-pyridine, *J* = 6.0 Hz), 8.60 (s, 2 H, α-indole), 6.8–8.1 (m, 10 H, benzenoid).

Chemical and Spectral Characterization of Structures in Scheme II. A. Demonstration of an Oxidizable Intermediate 3 in the Conversion of 2 → 4. Compound **2** in 2-methoxyethanol–acetonitrile–aqueous 2 N NaOH (1:1:2 v/v) was converted to the blue dye **4** in the presence of air, λ_{max} 393 nm (ε 1.4 × 10^4), 575 (1.4 × 10^4). When the same solutions of **2** and NaOH were deoxygenated with argon (5 min) prior to mixing, there resulted a green solution with λ_{max} 367 nm (rel intensity 10) and 575 (rel intensity 1) (**2** → **3**). The 575-nm band was attributed to **4** resulting from incomplete deoxygenation. This solution upon exposure to air immediately turned blue, λ_{max} 393 and 575 nm (rel intensities 1:1) (**3** → **4**).

B. Demonstration of Demethylation in the Conversion of 4 → 5. A blue solution of **4** in 1.8 N methanolic KOH became red [after 16 h, λ_{max} 525 nm (ε 3.3 × 10^4) (**4** → **5**)]. Treatment of **2** in methanol (1 ml) with 2.5 N NaOH (aqueous) (9 ml) for 1 h gave a red solution of **5**, λ_{max} 525 nm. A sample of **7a** (prepared by catalytic dehydrogenation of **1a**) in 10% methanol–1.8 N NaOH (aqueous) showed the same spectral characteristics as **5** derived from **4**, λ_{max} 521 nm (ε 3.6 × 10^4). An acidified solution of **5** derived from **4** showed λ_{max} 546 nm (ε 1.5 × 10^4) (**5** → **7**) and an acidic solution of **7a** showed λ_{max} 540 nm (ε 2.6 × 10^4) (**7a** → **7**). The lower extinctions of **5** and **7** derived from **4** were attributed to side reactions.[8] On diluting a methanolic solution of **2** tenfold with 1:1 (v/v) concentrated HNO_3–H_2O there was obtained a red solution, λ_{max} 547 nm (ε 2.1 × 10^4) (**2** → **8**). A blue solution of **4** obtained by diluting a methanolic solution of **2** tenfold with 2.5 N NaOH (aqueous), upon acidification with 1:1 (v/v) concentrated HNO_3–H_2O gave a red solution, λ_{max} 546 nm (ε 1.6 × 10^4) (**4** → **8**). Compound **8** was prepared from **2** in the absence of oxygen using HNO_3 and converted to **4** with 2 N NaOH (aqueous) in the absence of oxygen.

TLC Evidence for Structures in Scheme II. Compound **2** (1 g, 0.02 mol) was dissolved in 60 ml of 0.33 N methanolic KOH. The blue solution was stirred in air for 30 min, giving a red solution. The methanolic solution was evaporated. The solid was triturated with 50 ml of water and extracted with benzene. The remaining violet solid, insoluble in benzene and water, was dissolved in acetone to yield a yellow-orange solution. TLC on silica gel (acetone) of the benzene- and the acetone-soluble materials each showed one major spot (R_f 0.5 for the benzene-soluble product and 0.7 for the acetone-soluble product). A minor spot in each TLC indicated that each of the materials was contaminated with the other. Evaporation of an aliquot of the benzene soluble product on the probe of the mass spectrometer and subsequent analysis showed a major *m/e* 321 (**7a**) with a weaker peak *m/e* 323 assigned to the contaminant. The acetone-soluble product showed a major *m/e* 323. The benzene solution containing **7a** was extracted with 1:4 (v/v) concentrated HCl–H_2O and the purple acidic extract was evaporated in a stream of air to dryness to obtain a dark purple solid. The NMR spectrum of this sample revealed all of the resonances of the dihydrochloride **7**, which was obtained catalytically (method A). The characteristic quaternary methyl resonance of **2** (δ 4.0) was weak, corresponding to <10 mol %. Furthermore, the triarylmethinyl proton (δ 6.0) was not detected.

Kinetics of Alkylation of Diindolylpyridylmethanes. Into a 50-ml volumetric flask was placed 45 ml of 1:1 (v/v) 2-methoxyethanol and acetonitrile solvent mixture and the flask was thermostated at 30 °C. A solution of diindolylpyridylmethane (ca. 10^{-2} M) in the solvent mixture was added followed by methyl iodide (0.5 ml, 1.1 g). The flask was filled to the mark with thermostated solvent mixture. Periodically a 1-ml aliquot was withdrawn, placed in a 3-ml cuvette, and treated with 1 ml of 2 N NaOH (aqueous). After 2 min the absorbance was read at the appropriate λ_{max} (see Table II). The pseudo-first-order rate constants were calculated from $k = t^{-1} \ln (OD_\infty - OD_0)/(OD_\infty - OD_t)$ and second-order rate constants were obtained by dividing by $[CH_3I]$.

When the rate of alkylation of the 5-cyano compound **1h** was determined, the procedure had to be modified owing to the instability of the blue dye analogous to **4**. After a 1-ml aliquot was taken and treated with 1 ml of 2 N NaOH (aqueous), the solution was allowed to stand for 18 h (overnight) prior to reading the absorbance. During this period the solution became red (structure corresponding to **5**) and the absorbance was read at 532 nm.

Kinetics of Alkylation of Substituted Pyridines. Pyridine or a substituted pyridine (0.16 mmol) was dissolved in methanol-d_4 (0.4 ml), placed in an NMR tube, and thermostated at 30 °C for 10 min. To the solution was added 22.7 mg (0.16 mmol) of methyl iodide using a 10-μl syringe as a weight buret. Measures were taken to ensure thorough mixing. The samples were maintained at 30 °C in a constant-temperature bath and read periodically in the NMR spectrometer for short periods of time at 33 °C. Where the kinetic runs required extended reaction times, the samples were quenched overnight in dry ice and thawed rapidly the following morning. Periodic determination was made of the NMe/MeI resonance ratios as a function of time. Table IV summarizes the chemical shifts measured for the *N*-methylpyridines. The second-order rate constants were determined using the integrated form of the second-order rate law for reactants at equal concentrations (eq 1)

$$kt = x/a(a - x) \quad (1)$$

where $x(a - x)$ is the ratio of the *N*-methyl integral to the methyl iodide integral and *a* is the methyl iodide concentration determined by weight at $t = 0$. Molarity of the methyl iodide was calculated assuming a volume of 0.4 ml with no adjustment for volume changes upon mixing. The run-to-run reproducibility was ca. 10% of the rate constant.

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Registry No.—**1a**, 21182-09-2; **1b**, 21182-15-0; **1c**, 1053-39-0; **1d**, 57637-71-5; **1e**, 57637-72-6; **1f**, 57637-73-7; **1g**, 57637-74-8; **1h**, 57637-75-9; **1i**, 57637-76-0; **1j**, 57637-77-1; **1k**, 57637-78-2; **1l**, 57637-79-3; **1m**, 21182-11-6; **2**, 57637-80-6; **3**, 57637-81-7; **4**, 57637-82-8; **5**, 57637-83-9; **7a**, 1099-94-1; **7a** 2HCl, 57637-84-0; **9**, 57637-85-1; indole, 120-72-9; 4-pyridinecarboxaldehyde, 872-85-5; 5-cyanoindole, 15861-24-2; 1-methylindole, 603-76-9; benzyl chloride, 25168-05-2; methyl iodide, 74-88-4.

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A Synthetic Approach to the Cephalotaxine Skeleton

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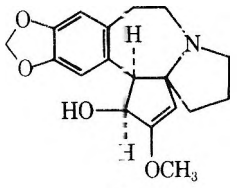
Several possible routes to the synthesis of the alkaloid cephalotaxine have been explored. Friedel–Crafts cyclization of 1-[2-(3,4-methylenedioxyphenyl)ethyl]pyrrole-2-carboxylic acid, followed by reduction with hydrogen over rhodium on charcoal, gave 8,9-methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine.

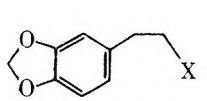
The alkaloid cephalotaxine (I), found in the plum yew, has been assigned an absolute structure based on a combination of chemical, spectral, and x-ray diffraction data.[1–6]



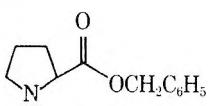
I

Esters of cephalotaxine derived from substituted malic and tartaric acids are known as harringtonines,[7–10] and are of interest because of their antitumor properties.[11] With a view to potential medicinal applications, work was begun in the fall of 1971 on the synthesis of the parent ring system, which, if successful, could be extended to other alkaloids in this series.

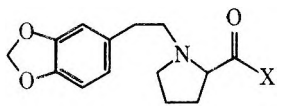
Treatment of 1,2-methylenedioxybenzene (II) with bromine gave 3,4-methylenedioxybromobenzene (III), as well as a small amount of 4,5-methylenedioxy-1,2-dibromobenzene (IV).[12] Generation of the Grignard reagent from the bromide III, followed by the addition of ethylene oxide, formed 3,4-methylenedioxyphenethyl alcohol (V). Refluxing alcohol V with phosphorus tribromide then produced 4-(2-bromoethyl)-1,2-methylenedioxybenzene (VI). Alkylation of benzyl prolinate (VII) by the bromide VI went smoothly; the intermediate benzyl ester (VIII) was not isolated, but was hydrogenated to the parent acid (IX).



V, X = OH
VI, X = Br



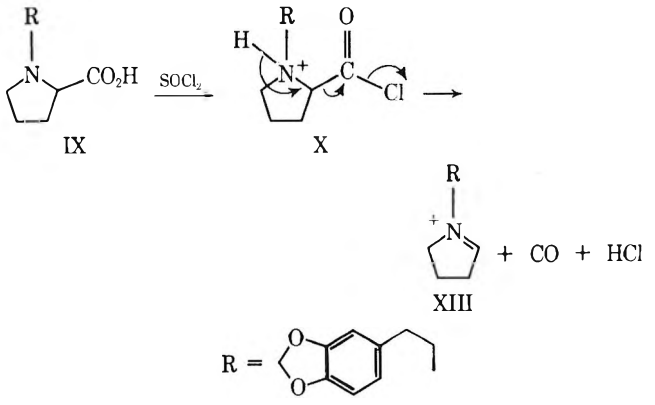
VII



VIII, X = $OCH_2C_6H_5$
IX, X = OH
X, X = Cl

The next step, Friedel–Crafts cyclization of compound IX, rather surprisingly failed because decarbonylation of the proline carboxyl group occurred with remarkable ease when attempts were made to prepare the acid chloride X. Interestingly, the treatment of proline (XI) with thionyl chloride has been said to give prolyl chloride hydrochloride (XII); unfortunately, no analytical or spectral data were provided to support the assigned structure.[13] By contrast, two other reports on the preparation of amino acid acyl chloride hydrochlorides are known and appear to be correct.[14,15] Treatment of acid IX with thionyl chloride, phosphorus trichloride, or oxalyl chloride yielded in all cases a new compound (XIII). The structure assigned to XIII was supported by the absence of a carbonyl group in the infrared and a correct proton count in the nuclear magnetic resonance spectrum for both the methylenedioxyphenylethyl and prolyl groups. These results can be explained by postulating the existence of a "reverse-Koch" reaction (Scheme I). Here, we assume the initial conversion of the acid IX to the desired acyl chloride X, which then undergoes decomposition either by nucleophilic attack or by internal rearrangement to yield the iminium chloride XII. Some support for this idea was found when it was observed that a solution of IX in methylene dichloride at −70 °C on treatment with trifluoroacetic acid evolved carbon monoxide. The same result was obtained when other modes of ring cyclization were tried with IX, for example, treatment

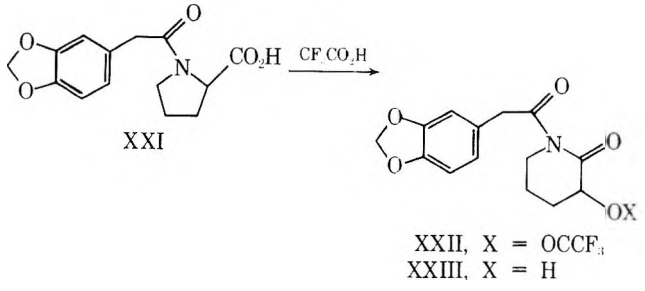
Scheme I. The Reverse-Koch Mechanism



with polyphosphoric acid or a dimethylformamide–sulfur trioxide complex.

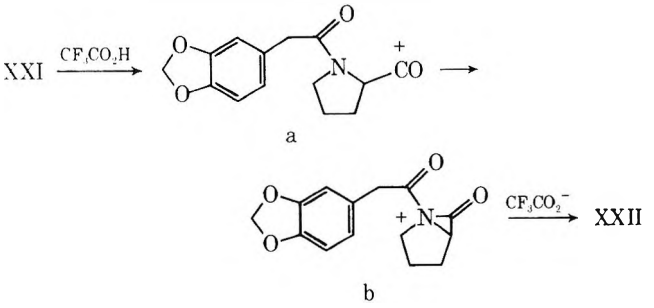
In an alternative approach, piperonal (XIV) was reduced in a Parr shaker to 3,4-methylenedioxybenzyl alcohol (XV), which on treatment with hydrogen bromide–hydrobromic acid produced the corresponding bromide (XVI). Heating XVI with sodium cyanide in dimethyl sulfoxide afforded 3,4-methylenedioxyphenylacetonitrile (XVII); subsequent hydrolysis in ethanol–water containing sodium methoxide gave 3,4-methylenedioxyphenylacetic acid (XVIII). This route from aldehyde XIV to acid XVIII is essentially the same as one already described in the literature;[16] however, our modification has the advantage that a low-pressure hydrogenation step is used on XIV, neither compounds XVI and XVII are isolated, and the overall yield of acid XVIII is quite high.

The coupling of acid XVIII to proline or proline esters was carried out by a variety of standard peptide techniques. It was found that optimum yields were obtained using an in situ formation of 2,4,5-trichlorophenyl 3,4-methylenedioxyphenylacetate (XIX), followed by the addition of thallium prolinate (XX) to form *N*-(3,4-methylenedioxyphenylacetyl)proline (XXI). An attempt to cyclize XXI with trifluoroacetic acid afforded two new products (XXII and XXIII). Compound XXII gave a negative ferric

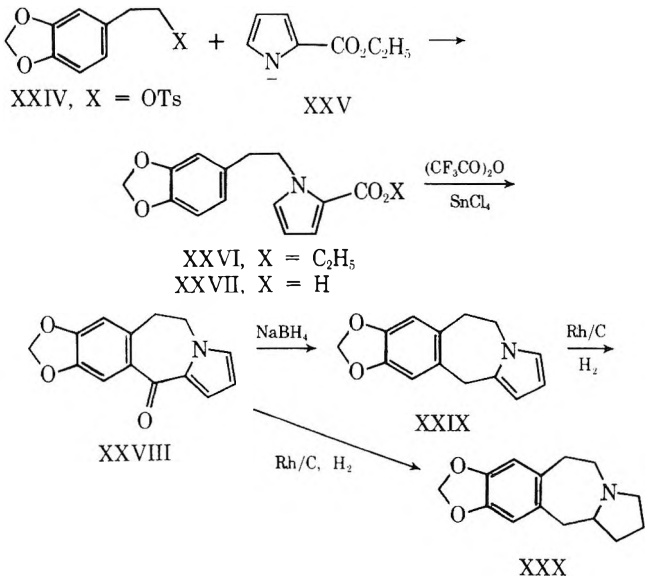


chloride test, and possessed absorptions at 1795, 1657, and 1638 cm^{-1} in the infrared. The very high carbonyl stretch at 1795 cm^{-1} in potassium bromide is characteristic of a trifluoroacetic ester, which is consistent with the unstable nature of this compound. Indeed, on recrystallization from moist solvents, or on preparative thin layer chromatography, XXII readily changed into XXIII. The latter product showed a broad band at 3300 cm^{-1}, as well as the disappearance of the 1795-cm^{-1} absorption. Other carbonyl absorptions were noted at 1760 (weak and sharp) and 1680 cm^{-1} (broad and very strong). The former can be attributed to an imide,[17] while the latter is probably due to two superimposed peaks, which, to be consistent with the rather long wavelength, are amide or hydrogen bonded carbonyls. This suggestion was confirmed by a shift to 3500, 1755, and 1715 cm^{-1}, respectively, when the spectrum was redetermined in chloroform. Further, in the nuclear magnetic resonance spectrum of XXIII, a single, exchangeable proton was detected at δ 6.4, which suggested a chelated hydroxyl proton such as –COCHOH–. Compound XXIII still contains the methylenedioxy group, seen at δ 6.0, as well as three aromatic protons at δ 6.6; so cyclization to a seven-membered ketone can be disregarded. These results can be rationalized by postulating the formation of a carbonium ion a that cyclizes to b; nucleophilic attack by trifluoroacetate ion then forms the observed product XXII (and, on hydrolysis, XXIII) (Scheme II). This type of ring expansion has been noted before, i.e., the acid-catalyzed conversion of 2-chloromethyl-*N*-methylproline to 3-chloro-*N*-methylpiperidine.[18,19]

Scheme II. The Carbonium Ion Mechanism



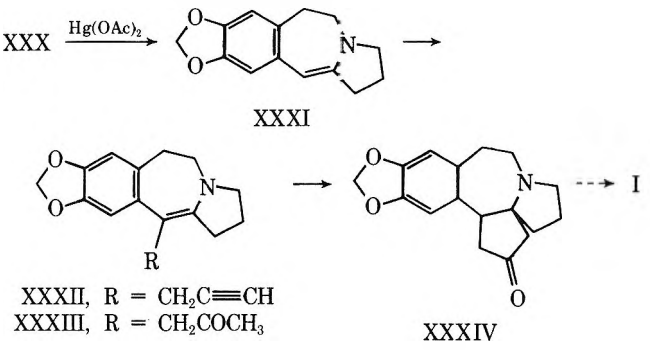
On the principle that the basicity of the proline nitrogen is the cause of the above undesired sequences, an alternative solution could be formulated in terms of a pyrrole intermediate. Thus, the alcohol V was converted into the tosylate XXIV and on addition of sodium 2-carbethoxypyrrole (XXV) there was obtained the pyrrole ester XXVI, which, without isolation, was hydrolyzed to the parent acid XXVII. Cyclization of the acid XXVII to the benzazepine



XXVIII was smoothly effected with trifluoroacetic anhydride–stannic chloride. A variety of reaction conditions were tried in order to either selectively reduce the pyrrole ring or the keto group in compound XXVIII, but only limited success was achieved. For example, sodium borohydride treatment of XXVIII gave the hydrogenolyzed benzazepine XXIX. The intermediate alcohol was easily detected by thin layer chromatography, as the spot attributed to it turned red on exposure to air. Similar deoxygenations have been seen previously in this heterocyclic system.[22] By contrast, the pyrrole ring in compounds XXVII or XXIX was rapidly reduced by a rhodium on charcoal

catalyst and the crystalline pyrrolidine (XXX) was produced in nearly quantitative yield. After the completion of this work, the same compound was obtained by another group in the form of a labile oil.[23] The reported spectral properties for this latter material were essentially identical with those measured on crystalline XXX.

The last stage in the synthesis called for the conversion of the tetracyclic base XXX via mercuric acetate oxidation to the enamine XXXI. After isolation, the desired intermediate XXXI was found to be unstable in chlorinated solvents and decomposed on standing. The same product has now been made by an alternative synthesis and a comparison of samples showed their mutual identity.[24] Reaction of XXXI with propargyl bromide formed the acetylene XXXII, which on mercury(II)-catalyzed hydration gave ketone XXXIII. Treatment of XXXIII with several acid catalysts neither produced pentacyclic ketone (XXXIV) nor any other cyclopentanone-containing product. These results are in complete agreement with a recent synthetic venture in this area,[24] but are in contrast with an earlier report.[23] Assuming that alternative modes of cyclization exist, the resulting ketone XXXIV would be converted by two or more steps into the desired alkaloid I.



At this point the work terminated, as we were unable to secure any support necessary to complete the synthesis or to begin analog studies. Note that within the past year two independent preparations of cephalotaxine have been published.[24,25] One of these is parallel to our route and intersects it at the enamine stage. Subsequently, no further effort is planned in this area.

Experimental Section[26]

3,4-Methylenedioxybromobenzene (III). Bromine vapor (187 g, 1.17 mol) was drawn through methylenedioxybenzene (143 g, 1.17 mol) in chloroform (600 ml) by an aspirator over a 4-h period. The original procedure calls for cooling the reaction mixture with an ice bath, but this gives a slow reaction rate.[12] Distillation afforded a small forerun of starting material, bp 57–68 °C (10 mm), followed by the product (216 g, 91%), bp 103–107 °C (10 mm). The residue in the still pot crystallized on cooling, and a recrystallization from methanol yielded a small quantity of 4,5-methylenedioxy-1,2-dibromobenzene, mp 86 °C.

3,4-Methylenedioxyphenethyl Alcohol (V). 3,4-Methylenedioxybromobenzene (80 g, 0.40 mol) was added dropwise with stirring to magnesium (10 g, 0.44 mol) in anhydrous tetrahydrofuran (300 ml) under dry nitrogen. The mixture was then refluxed for 0.5 h and cooled to 0 °C, and ethylene oxide (21.8 ml, 19.3 g, 0.44 mol) was distilled into the reaction flask at such a rate that the temperature never rose above 5 °C. When the addition was complete, the mixture was refluxed for 1 h and then worked up by acidification and extraction. Distillation gave a small forerun of methylenedioxybenzene (6 g), followed by the product (49.4 g, 75%), bp 115–125 °C (0.2 mm), mp 21–22 °C [lit. bp 120–122 °C (2.5 mm)].[27]

4-(2-Bromoethyl)-1,2-methylenedioxybenzene (VI). To a solution of the aforementioned alcohol (45 g, 0.3 mol) in ethyl ether (300 ml) cooled to 10 °C, phosphorus tribromide (35 g, 0.13 mol) was added dripwise while maintaining the temperature below 10 °C. The reaction mixture was then refluxed for 1 h, followed by work-up and distillation to yield the product (44.4 g, 80%), bp 142–144 °C (6 mm) [lit. bp 144 °C (6 mm)].[28]

Benzyl *N*-2-(3,4-Methylenedioxyphenyl)ethylprolinate (VIII). A solution of 4-(2-bromoethyl)-1,2-methylenedioxybenzene (22.9 g, 0.10 mol), benzyl prolinate hydrochloride (41 g, 0.20 mol),[29] potassium carbonate (20 g, 0.20 mol), and potassium iodide (23 g, 0.20 mol) in dimethylformamide (40 ml) was heated to 100 °C until the evolution of carbon dioxide ceased. Work-up by extraction gave the product (25.4 g, 75%) as a nearly colorless yellow oil.

***N*-2-(3,4-Methylenedioxyphenyl)ethylproline (IX).** The benzyl ester (6.15 g, 0.0175 mol) was hydrogenated at atmospheric pressure using 10% palladium on charcoal catalyst (1 g) in methanol (200 ml). After the uptake of hydrogen had ceased, the catalyst was removed, the solvent evaporated, and the residue recrystallized from ethyl acetate–methanol to yield the product (3.8 g, 84%): mp 195–197 °C; ir (KBr) 3010, 2840, 1625, 1490, and 1250 cm^{-1}; NMR (D_2O + NaOD) δ 6.5 (m, 3), 5.7 (s, 2), and 3.9–1.7 (11).

Anal. Calcd for $C_{14}H_{17}NO_4$ (263.17): C, 63.87; H, 6.51; N, 5.32. Found: C, 64.38; H, 6.60; N, 5.04.

3,4-Methylenedioxybenzyl Bromide (XVI). Piperonal (100 g, 0.667 mol) was dissolved in methanol (200 ml) and hydrogenated for 12 h in a Parr shaker using platinum oxide (300 mg) activated with ferric sulfate (150 mg, 1.00 mmol) and sodium methoxide (108 mg, 2.00 mmol). On removal of the solvent in vacuo, the crystalline residue, mp 57 °C, was treated with fuming hydrobromic acid prepared by saturating concentrated hydrobromic acid with gaseous hydrogen bromide at 0 °C. After about 1 min, the oil that formed resolidified into a mass of needles, which were filtered and dried in vacuo (140 g, 98%), mp 49–50 °C.

3,4-Methylenedioxyacetonitrile (XVI). 3,4-Methylenedioxybenzyl bromide (21.6 g, 0.1 mol) was added in portions to a stirred suspension of sodium cyanide (10 g, 0.2 mol) in dimethyl sulfoxide (20 ml)–water (5 ml) at such a rate that the temperature did not rise above 40 °C. When the last portion of bromide was added, the colorless slurry turned into a thick paste. Dilution with water (100 ml) and work-up by extraction yielded the product as a partially crystalline, pale yellow oil, which was used without further purification in the next step. A small portion was distilled for spectral purposes, bp 135–140 °C (5 mm).

3,4-Methylenedioxyphenylacetic Acid (XVIII). The aforementioned nitrile was refluxed overnight in ethanol (50 ml) containing water (5 ml) and sodium methoxide (10 g, ca. 0.2 mol). Work-up by extraction followed by crystallization from water and recrystallization from benzene yielded colorless needles (14.7 g, 82%), mp 128–129 °C (lit. mp 128–129 °C[16]).

Thallium Prolinate (XX). Proline (11.5 g, 0.100 mol) was suspended in refluxing ethanol (50 ml) and treated with thallium ethoxide (7.2 ml, 0.10 mol) and the resulting solution was cooled to 6 °C and diluted with ether (75 ml). The resulting mass of colorless crystals was collected and dried in vacuo (29.9 g, 94%).

***N*-(3,4-Methylenedioxyphenylacetyl)proline (XXI).** To a stirred solution of 3,4-methylenedioxyphenylacetic acid (1.8 g, 10 mmol) dissolved in ethyl acetate (50 ml), *N,N'*-dicyclohexylcarbodiimide (2.1 g, 10 mmol) was added, followed by 2,4,5-trichlorophenol (2.6 g, 10 mmol). A white precipitate of *N,N'*-dicyclohexylurea immediately formed, after which thallium prolinate (3.18 g, 10.0 mmol) was added and the mixture allowed to stand for 20 h. A solution of sodium iodide was added to precipitate thallium ion; then the mixture was filtered and extracted with saturated sodium bicarbonate. The aqueous phase was neutralized, and the resulting crude product was collected, recrystallized from benzene, and sublimed (1.8 g, 65.5%): mp 165–168 °C dec; ir (KBr) 2700, 2570 (broad), 1735, 1595, and 1200 cm^{-1}; NMR ($CDCl_3$) δ 9.7 (s, 1), 6.6 (s, 3), 6.0 (s, 2), 4.6 (b, 1), 3.7 (s, 2), 3.6 (b, 2), and 2.1 (b, 4).

Anal. Calcd for $C_{14}H_{15}NO_5$ (277.16): C, 60.63; H, 5.45; N, 5.05. Found: C, 60.32; H, 5.39; N, 4.81.

Reaction of *N*-(3,4-Methylenedioxyphenylacetyl)proline with Trifluoroacetic Anhydride. The aforementioned acid (1.35 g, 5.00 mmol) was dissolved in tetrahydrofuran (40 ml) containing trifluoroacetic anhydride (2 g, ca. 10 mmol). After 15 min, the solvent was removed and the residue was recrystallized from tetrahydrofuran–ether to yield an unstable, minor component (XXII). On exposure to air or on heating the product rearranged into compound XXIII: ir (KBr) 1795, 1657, and 1638 cm^{-1}; negative ferric chloride test.

The mother liquors were evaporated and the residue was recrystallized from chloroform to yield the second component (XXIII): mp 165–168 °C dec; ir (KBr) 3300 (broad), 1760 (sharp, weak), and 1680 cm^{-1} (broad, very strong); ir ($CHCl_3$) 3500, 1755, and 1715

cm^{-1}; NMR ($CDCl_3$) δ 6.85 (s, 3), 6.41 (broad, exchangeable with D_2O, 1), 6.02 (s, 2), 4.55 (s, 1), 3.6–4.2 (m, 1), 2.15–3.5 (m, 4), and 1.9–2.15 (pentet, 3). No satisfactory analysis could be obtained owing to the labile nature of this product.

2-(3,4-Methylenedioxyphenyl)ethyl Tosylate (XXIV). Pyridine (8.0 g, 0.1 mol) and 3,4-methylenedioxyphenethyl alcohol (16.5 g, 0.10 mol) were dissolved in dichloromethane (50 ml) and the solution was dried by distilling the solvent until the vapor temperature reached 40 °C. After cooling to 0 °C, *p*-toluenesulfonyl chloride (20 g, 0.105 mol) was dissolved in dichloromethane (30 ml), filtered, and then added to the other reactants. After standing for 1 day at room temperature, the reaction mixture was cooled to −6 °C and filtered to remove the pyridine hydrochloride (ca. 10 g, very hydroscopic). Work-up by extraction with dilute hydrochloric acid, followed by crystallization from ether at −70 °C, gave the product (29.2 g, 94%): mp 59–60 °C; ir (KBr) 2900, 1360, 1165, and 770 cm^{-1}; NMR ($CDCl_3$) δ 7.7 (d, 2), 6.6 (m, 3), 5.9 (s, 2), 4.2 (t, 2), 2.8 (t, 2), and 2.4 (s, 3).

Anal. Calcd. for $C_{16}H_{16}O_5S$ (320.23): C, 60.00; H, 5.00; S, 10.00. Found: C, 59.77; H, 5.18; S, 9.80.

***N*-[2-(3,4-Methylenedioxyphenyl)]ethylpyrrole-2-carboxylic Acid (XXVII).** A solution of 2-carbethoxypyrrole (39 g, 0.36 mol) in diethylene glycol dimethyl ether (diglyme) was added dropwise to a stirred suspension of sodium hydride (50% suspension in mineral oil, 16 g, 0.36 mol) in diglyme (200 ml) under a nitrogen blanket. When all of the sodium hydride has reacted, the aforementioned tosylate (11.5 g, 0.358 mol) was added and the mixture was heated for 3 days at 70 °C. After removal of most of the solvent in vacuo, the residue was saponified by refluxing in 2 M ethanolic potassium hydroxide (250 ml) overnight. Work-up by extraction as before and recrystallization from benzene gave the product (59.0 g, 63.5%): mp 127–130 °C; ir (KBr) 2700, 2630, 2560, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 11.1 (broad, 1), 7.3 (pair of doublets, 1), 6.7 (m, 4), 6.2 (pair of doublets, 1), 6.0 (s, 2), 4.55 (m, 2), and 3.05 (m, 2).

Anal. Calcd for $C_1H_{13}NO_4 \cdot \frac{1}{2}H_2O$ (248.16): C, 62.90; H, 5.24; N, 5.20. Found: C, 62.70; H, 4.77; N, 5.16.

11-Oxo-8,9-methylenedioxy-6-hydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXVIII). Trifluoroacetic anhydride (25 ml, ca. 0.2 mol) was added with stirring to a suspension of *N*-[2-(3,methylenedioxyphenyl)]ethylpyrrole-2-carboxylic acid (25.9 g, 0.100 mol) in ethanol-free chloroform (500 ml) under nitrogen. The mixture turned deep red within 5 min, at which time thin layer chromatography indicated that the starting acid was absent in the reaction. After the mixture was cooled to 0 °, stannic chloride (32.7 ml, 0.300 mol) was added dropwise, and the mixture allowed to come to room temperature and stand for 4 h. After destruction of the stannic chloride–product complex by the addition of aqueous ammonia, the organic layer was separated and the solvent was removed in vacuo. The residue was recrystallized from ethyl acetate to give the product (21.1 g, 88%): mp 121–123 °C; uv (acetonitrile) 236 nm (ϵ 32 000), 277 (16 000), and 240 (38 000); ir (KBr) 3070, 2960, 2910, 2780, 1640 (weak), 1595 (strong), and 1475 cm^{-1}; NMR ($CDCl_3$) δ 5.78 (s, 1), 7.4 (m, 1), 6.9 (m, 1), 6.7 (s, 1), 6.3 (m, 1), 6.1 (s, 2), 4.4 (d, 1), 4.3 (d, 1), and 3.2 (m, 2).

Anal. Calcd. for $C_{14}H_{11}NO_3$ (241.16): C, 69.70; H, 4.60; N, 5.81. Found: C, 70.50; H, 4.61; N, 5.71.

8,9-Methylenedioxy-1,6-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXIX). The aforementioned benzazepine (1.2 g, 0.05 mol) was refluxed overnight in diglyme (200 ml) containing sodium borohydride (12 g, large excess). At this time the intermediate alcohol, which was easily detectable by thin layer chromatography as a spot that rapidly turned dark red, was virtually absent. The mixture was then poured into water (500 ml), filtered, and recrystallized from methanol to yield the pale yellow product (11 g, 97%). Recrystallization from benzene–petroleum ether and sublimation (95 °C, 0.02 mm) gave a pure sample: mp 120–122 °C; ir (KBr) 3130 (sharp), 2960, 2890, 2780, and 15 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (d, 2), 6.4 (t, 1), 5.9 (m, 2), 5.8 (s, 2), 4.1 (pair of doublets), 3.8 (s, 2), and 3.0 (pair of doublets).

Anal. Calcd for $C_{14}H_{13}NO_2$ (203.23): C, 70.91; H, 6.45; N, 6.89. Found: C, 70.61; H, 6.44; N, 6.82.

8,9-Methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (XXX). From XXIX. The aforementioned pyrrole (227 mg, 1 mmol) was hydrogenated at atmospheric pressure in acetic acid (40 ml) using 5% rhodium on charcoal catalyst (50 mg). After 1 h the hydrogen uptake dropped markedly, and the reaction mixture was worked up. The product was converted to the hydrochloride salt by addition of a few drops of concentrated hydrochloric acid to a solution of the acetate salt in an ether–ethanol solution to give white needles (250 mg, 97%), mp 260–270 °C dec (lit. mp 265–266 °C dec).[23]

From XXVIII. The ketopyrrole (480 mg, 2.00 mmol) was dissolved in hot 95% ethanol (200 ml) and the solution was added to a stirred suspension of presaturated 5% rhodium on charcoal (10 g) in 95% ethanol (20 ml) containing perchloric acid (10 drops). After approximately 1 day, 8 equiv (17.9 ml) of hydrogen had been absorbed and no starting material or intermediate alcohol could be detected by thin layer chromatography. After filtration, the solvent was removed in vacuo, and the residue was extracted into chloroform following neutralization of the salt. The chloroform was evaporated and the residue was crystallized from methanol, followed by sublimation to give the product (450 mg, 98%), mp 70–71 °C. The spectral properties of this compound were identical with those reported in the literature.[23] Addition of hydrochloric acid to a solution of the amine in 2-propanol afforded the salt, mp 260–270 °C dec.

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Registry No.—II, 274-09-9; III, 2635-13-4; IV, 5279-32-3; V, 6006-82-2; VI, 57587-02-7; VII HCl, 16652-71-4; VIII, 57587-03-8; IX, 57587-04-9; XIV, 120-57-0; XVI, 2606-51-1; XVII, 4439-02-5; XVIII, 2861-28-1; XX, 57587-05-0; XXI, 57587-06-1; XXII, 57587-07-2; XXIII, 57587-08-3; XXIV, 57587-09-4; XXVII, 57587-10-7; XXVIII, 57587-11-8; XXIX, 57587-12-9; XXX, 35667-18-6; XXX HCl, 35667-19-7; 3,4-methylenedioxyphenylacetic acid, 2861-28-1; 2,4,5-trichlorophenol, 95-95-4; trifluoroacetic anhydride, 407-25-0; *p*-toluenesulfonyl chloride, 98-59-9; carbethoxypyrrole, 2199-43-1.

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The Isomeric Ethylene Selenodithiocarbonates

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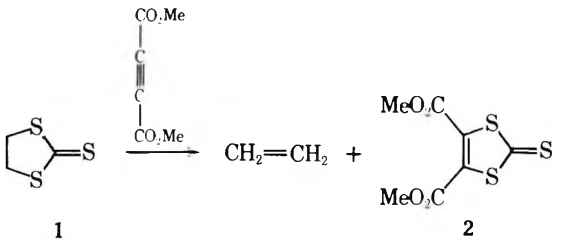
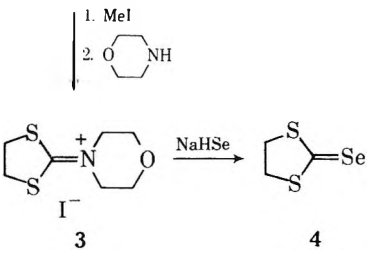
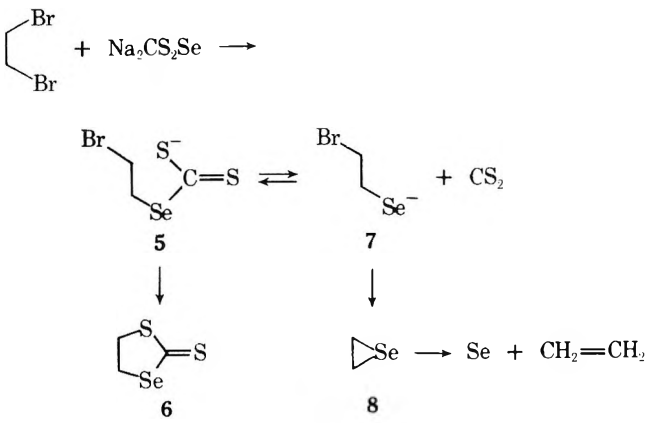
Syntheses of 1-selena-3-thiolane-2-thione (**6**) and 1,3-dithiolane-2-selone (**4**) are described. Both **6** and **4** react with dimethyl acetylenedicarboxylate to give a mixture of the isomeric esters **9** and **10**. The esters are thermally interconvertible in the presence of dimethyl acetylenedicarboxylate.

It has been known since 1965 that ethylene trithiocarbonate (**1**) reacts with dimethyl acetylenedicarboxylate to give ethylene and the isotrithione diester **2**;[1] the latter ester has acquired considerable importance recently as a readily prepared precursor of tetrathiafulvalene.[2] A 1970 study of the action of dimethyl acetylenedicarboxylate on mixed sulfur–oxygen analogues of ethylene trithiocarbonate indicated that the dithio ester function (–S–C=S) was essential for the success of the reaction.[3]

In connection with the broad problem of the synthesis of selenium analogues[4] of tetrathiafulvalene, we have studied the synthesis and dipolar addition reactions of various selenium analogues of ethylene trithiocarbonate. This paper describes the synthesis and some chemistry of the two isomeric monoselenium analogues, 1-selena-3-thiolane-2-thione (**6**) and 1,3-dithiolane-2-selone (**4**).





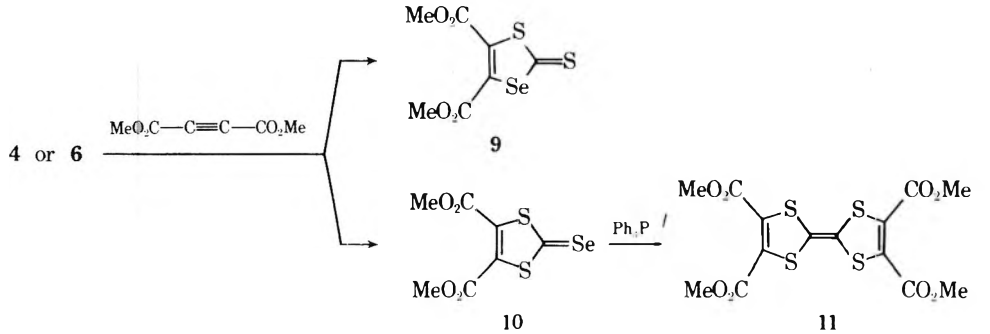


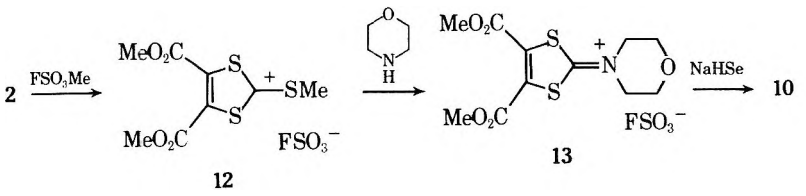
Results

Synthesis of the Isomeric Ethylene Selenodithiocarbonates. The synthesis of ethylene trithiocarbonate (**1**) from ethylene dibromide and sodium trithiocarbonate was reported more than a century ago, and affords a good yield of **1**.[5] The reaction of ethylene dibromide with the recently described selenodithiocarbonate ion[6] was expected to take place in a similar manner, the anticipated major product being the thione isomer **6** because of the superior nucleophilicity of the selenium atom of the attacking anion. The yellow thione **6**, mp 50 °C, was in fact isolated in ca. 2% yield from this reaction. The major reaction course led to the precipitation of red selenium (75%), accompanied by the vigorous evolution of ethylene. The latter process can be rationalized by assuming that the initially formed monoalkylated anion **5** is in equilibrium with carbon disulfide and the β-bromoethylselenide ion (**7**); the latter can rapidly cyclize to the extremely thermolabile[7] ethylene episelenide (**8**).

Ethylene trithiocarbonate is easily converted, via its methiodide, into the known morpholinium iodide **3**;[8] reaction of salt **3** with aqueous sodium hydrogen selenide[9] afforded (63%) the coral-red selone **4**, mp 44–45°. Solutions of **4** in nonpolar solvents were a beautiful purple in color, owing to a fairly strong selenocarbonyl absorption maximum at 570 nm.[10]

Reaction of the Ethylene Selenodithiocarbonates with Dimethyl Acetylenedicarboxylate. Selone **4** reacted with dimethyl acetylenedicarboxylate in refluxing toluene to give, in good yield, a red crystalline product, mp 85 °C. Although this material seemed to be homogeneous by all ordinary criteria, including TLC, it was found to be a mixture of the isomeric esters **9** and **10**, which could be separated partially by very slow chromatography (over 2





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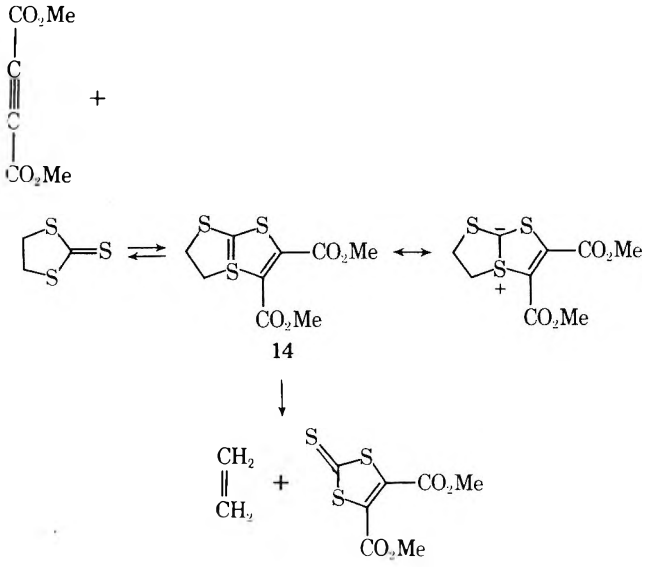
weeks) on silica. The pure components consisted of the expected yellow thione ester **9**, mp 102 °C, and the unexpected maroon selone ester **10**, mp 79 °C; the deep color of the latter was attributed to selone absorption at 540 nm. The reaction of thione **6** with dimethyl acetylenedicarboxylate afforded a similar mixture of the isomeric esters **9** and **10**.

The structure **10** assigned to the maroon ester was supported by its deselenation by triphenylphosphine to give the known[11] black tetracarbomethoxytetrathiafulvalene (**11**). Further confirmation of structure **10** was obtained by an unrelated synthesis. Thus, thione ester **2** was alkylated by methyl fluorosulfonate to give the salt **12**, which reacted with morpholine to give immonium salt **13**. Reaction of **13** with sodium selenide–acetic acid gave the maroon ester **10**.

Discussion

Although the reaction of dimethyl acetylenedicarboxylate with ethylene trithiocarbonate has been recognized as a 1,3-dipolar addition,[1,12] no discrete chemical intermediate has hitherto been proposed. We suggest that the bicyclic "tetracovalent" sulfur heterocycle **14** is produced initially,[13] and that this unstable species then either reverts reversibly to the starting materials, or collapses irreversibly to give the observed products.



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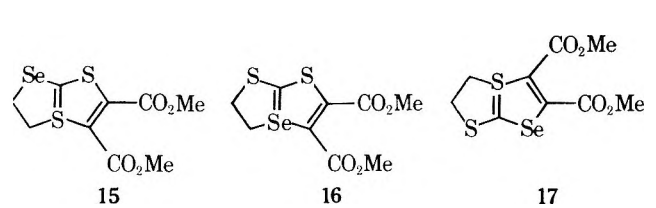
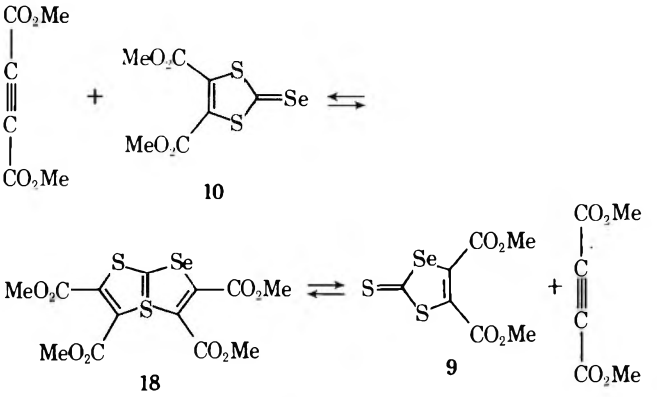
The analogous reaction of thione **6** to give a mixture of esters **9** and **10** is readily accommodated by this mechanism, since addition of the acetylene to either the –S–C=S or the –Se–C=S moiety of **6** is possible, giving rise to the different bicyclic intermediates **15** and **16**. On the other hand, the selone **4** would be expected to give only the thione ester **9** via intermediate **17**. The explanation of this apparent anomaly became clear when it was observed that, although esters **9** and **10** are quite stable in pure refluxing toluene, they are *interconverted* under the same conditions in the *presence of dimethyl acetylenedicarboxylate*. These facts point to the transient bicyclic tetraester **18** as the key species through which the isomers **9** and **10** equilibrate under the conditions of their formation from **4** and **6**.



15 16 17



10

18 9

Experimental Section

Melting points are uncorrected. Chromatography was carried out using dry column silica. All organic extracts were washed to neutrality and dried over anhydrous sodium sulfate. NMR spectra ($CDCl_3$ solutions containing tetramethylsilane as internal standard), ultraviolet spectra (cyclohexane solutions), and mass spectra were determined using JEOL-JNH-PS-100, Perkin-Elmer 202 and 270B spectrometers, respectively. Molecular ions containing selenium are reported based on ^{80}Se.

1-Selena-3-thiolane-2-thione (6). To a stirred solution of selenium dioxide (1 g) in 70% aqueous dioxane (20 ml) at 0 °C under nitrogen was added sodium borohydride (0.70 g) in portions. To the resulting sodium hydrogen selenide solution was added aqueous sodium hydroxide (0.4 g in 5 ml), followed by carbon disulfide (2 ml). To the resulting reddish-violet solution was added, at 0 °C, ethylene dibromide (3 g) in dioxane (10 ml). After 1 hr, the mixture was diluted with water and benzene, and the precipitated selenium (0.6 g, 75%) filtered off. The crude product from the benzene layer was subjected to chromatography (benzene–cyclohexane, 3:2). The residue from the initial fraction crystallized from hexane to give **6** (30 mg, ~2%): mp 50 °C; mass spectrum M^+ *m/e* 184 (100%); NMR δ 3.968–4.115 (m); λ_{max} 208 nm (log ε 3.97), 303 (4.10), 326 (4.08), 476 (1.82). Anal. Calcd for $C_3H_4S_2Se$: 183.8919. Found: 183.8919.

1,3-Dithiolane-2-selone (4). To a stirred aqueous solution (30 ml) of sodium hydrogen selenide[9] (from 0.50 g of selenium) under nitrogen was added 40 ml of benzene followed by the morpholinium iodide **3**[8] (0.317 g) in one portion. After 0.5 h the reddish-violet benzene layer was separated and the aqueous layer extracted with more benzene (2 × 25 ml). The residue from the benzene extracts was chromatographed (benzene–cyclohexane, 1:2) to yield selone **4** (0.190 g) as the major product. Recrystallization from ether–hexane yielded pure **4** (0.115 g, 63%) as small, coral-red needles: mp 44–45°; mass spectrum M^+ *m/e* 184 (100%); NMR δ 3.870 (s); λ_{max} 217 nm (log ε 3.65), 298 (3.96), 355 (4.11), 570 (2.08). Anal. Calcd for $C_3H_4S_2Se$: C, 19.68; H, 2.20. Found: C, 19.92; H, 2.39.

Reaction of 4 with Dimethyl Acetylenedicarboxylate (9 + 10). A mixture of selone **4** (1.14 g) and dimethyl acetylenedicarboxylate (1.1 ml) in dry toluene (15 ml) was refluxed for 1.5 h. Evaporation of solvent, followed by crystallization of the residue from methanol, yielded a 1:1 mixture of thione ester **9** and selone ester **10** (0.695 g, mp 85 °C) as orange-red crystals. Chromatography of the residue from the mother liquor (1:1 benzene–cyclohexane) followed by crystallization yielded more of the mixture of **9** and **10** (0.405 g; total yield 61%).

Separation of 9 and 10. The foregoing mixture of **9** and **10** (0.225 g) was chromatographed very slowly in the dark using benzene–cyclohexane (1:20). Evaporation of the first few milliliters of pure yellow eluate, followed by crystallization of the residue (MeOH), afforded pure thione ester **9** (0.05 g) as yellow needles: mp 102 °C; mass spectrum M^+ *m/e* 298 (100%); NMR δ 3.90 (two barely discernible singlets); λ_{max} 250 nm (log ϵ 3.75), 305, 360, 365 (3.97). Anal. Calcd for $C_7H_6O_4S_2Se$: 297.8872. Found: 297.8854.

The intermediate band gave a mixture of **9** and **10** while the last few milliliters of red eluate upon evaporation followed by crystallization (MeOH) afforded pure selone ester **10** (0.03 g): mp 79 °C; mass spectrum M^+ *m/e* 298; NMR δ 3.909 (s); λ_{max} 210 nm (log ϵ 4.33), 290, 295 (3.17), 392 (4.30), 540 (2.51). Anal. Calcd for $C_7H_6O_4S_2Se$: 297.8872. Found: 297.8860.

Thermal Behavior of 9. A yellow solution of thione diester (5 mg) **9** in toluene (0.2 ml) was refluxed for 1.5 h in the absence of light. Work-up of the yellow solution led to recovery of **9** (3 mg), ir, melting point.

Thermal Behavior of 10. A red solution of selone diester (6 mg) **10** in toluene (0.2 ml) was refluxed for 1.5 h in the absence of light. Work-up led to recovery of **10** (3 mg), ir, melting point.

Synthesis of 10. A mixture of **2** (50 g) and methyl fluorosulfonate (25 ml) in 1:1 methylene chloride–ether (100 ml) was refluxed with stirring to yield the thiolium salt **12** (72 g, quantitative), mp 125 °C. Anal. Calcd for $C_8H_9FO_7S_4$: C, 26.37; H, 2.49. Found: C, 26.36; H, 2.66.

A stirred suspension of the above salt **12** (72 g) in dry acetonitrile (50 ml) was cooled in ice, and was treated with morpholine (18 ml) dropwise. The clear solution was stirred at room temperature for 3 h. The crude immonium salt **13** (53 g) was precipitated with ether. Recrystallization from acetone yielded pure **13** (30 g), mp 115 °C. A second crop of slightly less pure **13** (20 g) was obtained from the mother liquor of crystallization. Anal. Calcd for $C_{11}H_{14}FNO_8S_3$: C, 32.75; H, 3.50. Found: C, 32.83; H, 3.64.

To a stirred suspension of immonium salt **13** (0.20 g) in benzene (75 ml) containing acetic acid (1 ml) under nitrogen was added sodium selenide (0.50 g) followed by water (20 ml). The benzene layer turned red instantly. After stirring for 1 h, the mixture was filtered (Celite), and the benzene layer was separated. Evaporation yielded a red gum (0.130 g) which was purified by chromatography followed by crystallization, to yield pure **10** (0.05 g, ~33%), identical (melting point, ir) with the sample from the cycloaddition.

Interconversion of 9 and 10. A mixture of thione ester **9** (0.007 g) and dimethyl acetylenedicarboxylate (0.005 g) in toluene (0.05 ml) was refluxed at 110 °C for 1.5 h. Chromatography of the reaction mixture led to the isolation of a mixture of **9** and **10** (0.005 g, approximately 2:1 as estimated by uv spectroscopy) which crystallized from methanol to yield 0.003 g, **9** + **10**, mp 80–82 °C. Similarly synthetic selone ester **10** (0.04 g) and dimethyl acetylenedicarboxylate (0.02 g) in toluene (0.50 ml) led to a mixture of **9** and **10** (0.034 g, 1:1 as estimated by uv spectroscopy).

Reaction of 10 with Triphenylphosphine (11). A solution of **10** (0.02 g) and triphenylphosphine (0.02 g) in benzene (5 ml) was refluxed for 1.5 h. The solvent was removed and the residue was chromatographed (benzene–cyclohexane, 1:1). The major dark reddish-brown band was eluted separately to yield, after evaporation and crystallization (MeOH), tetraester **11**, mp 165 °C, mass spectrum M^+ *m/e* 436, identical in all respects (ir, uv, TLC, mass spectrum) with authentic **11**.[11]

Reaction of 6 with Dimethyl Acetylenedicarboxylate. A mixture of **6** (0.05 g) and dimethyl acetylenedicarboxylate (0.03 g) in toluene (0.50 ml) was refluxed for 1.5 h. After work-up a 3:1 mixture of **9** and **10** (0.034 g) was isolated.

Acknowledgment. We thank the National Science Foundation for a grant (MPS 74-03279) in support of this work, and Dr. H. D. Hartzler of Du Pont for an authentic sample of **11**.

Registry No.—**2**, 7396-41-0; **3**, 2080-54-8; **4**, 57560-02-8; **6**, 57560-03-9; **9**, 57560-04-0; **10**, 57560-05-1; **11**, 26314-39-6; **12**, 57560-07-3; **13**, 57560-09-5; selenium dioxide, 7446-08-4; carbon disulfide, 75-15-0; ethylene dibromide, 106-93-4; sodium hydrogen selenide, 12195-50-5; dimethyl acetylenedicarboxylate, 762-42-5; methyl fluorosulfonate, 421-20-5; triphenylphosphine, 603-35-0.

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Notes

An Alternate Synthesis of Tetraselenafulvalene

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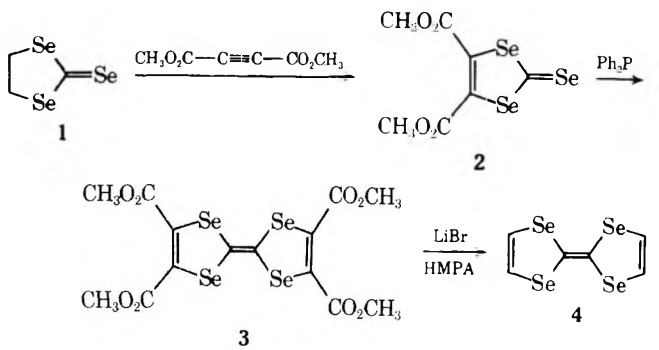
There has been much interest recently in the synthesis of tetraselenafulvalene (4, TSeF)[1] and its alkyl derivatives,[2] in view of the fact that these compounds are superior π donors in the preparation of highly conducting charge-transfer complexes. Only one synthesis of the parent TSeF has been reported to date.[1] We now report a convenient alternate synthesis of this compound, employing its previously unknown tetracarbomethoxy derivative 3 as an intermediate.

Ethylene triselenocarbonate (1)[3] reacted rapidly (10 min) with dimethyl acetylenedicarboxylate in toluene at 100°C to give (86%) deep red needles of the selone diester 2, mp 127°C. Triphenylphosphine coupling of 2 (10 min) in refluxing benzene, gave (75%) dark brown needles of tetracarbomethoxy TSeF (3), mp 145°C. Direct decarbomethoxylation of ester 3 was effected by lithium bromide in hot hexamethylphosphoramide (10 min, 150°C) to give (35%) tetraselenafulvalene (4) as pink plates, mp 133–134°C, identical in properties (melting point, uv, mass spectrum) with the previously reported material.

Several aspects of this new synthesis are worthy of note. The first of these is the greatly accelerated rate of reaction of dimethyl acetylenedicarboxylate with triselenocarbonate 1 as compared with that of ethylene trithiocarbonate, the latter compound requiring a 6-h reaction time at 110°C.[4] The second of these is the fact that a one-step lithium halide decarbomethoxylation has been reported previously only in the case of β-keto esters.[5] The conversion of 3 to 4 by this procedure suggests that it should be applicable to the decarbomethoxylation of related sulfur-containing esters. We are currently exploring the scope of the method with such esters.



1 2 3 4

Experimental Section

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Ultraviolet spectra (cyclohexane solutions) were recorded with a Perkin-Elmer Model 202 spectrometer. NMR spectra were run in $CDCl_3$ solution containing Me_4Si as internal standard, using a JEOL 100-MHz instrument. Mass spectra were obtained using a Perkin-Elmer Model 270 instrument. Molecular ions are based on ^{80}Se.

1,3-Diselenolane-2-selone (1). 1,3-Diselenolane-2-selone was prepared by the method of Henriksen.[3] Carbon diselenide (2 g) was treated with ethylene dibromide (2.2 g) in 10% aqueous dimethyl sulfoxide (120 ml) in the presence of 3 g of potassium carbonate under nitrogen to yield 1.1 g of 1, mp 100°C (lit.[3] mp 99–101°C), mass spectrum M^+ *m/e* 280 (85%).

4,5-Dicarbomethoxy-1,3-diselenole-2-selone (2). A mixture of 1 (0.772 g) and dimethyl acetylenedicarboxylate (0.4 ml) in toluene (3 ml) was heated on the steam bath for 10 min. Removal of solvent followed by crystallization of the residue from methanol afforded 2 (0.93 g, 86%): mp 127–128°C; mass spectrum M^+ *m/e* 394 (86%); NMR δ 3.88 s; λ_{max} (log ϵ) 217 nm (4.02), 235 (3.97), 252 sh (3.90), 405 (4.02), 562 (2.17).

Anal. Calcd for $C_7H_6O_4Se_3$: C, 21.50; H, 1.54. Found: C, 21.59; H, 1.72.

Tetracarbomethoxytetraselenafulvalene (3). To a boiling solution of 2 (0.120 g) in dry benzene (3 ml) under nitrogen was added a solution of triphenylphosphine (0.080 g) in benzene (3 ml) in portions, in the course of 10 min. The reaction mixture was concentrated and subjected to chromatography on silica, eluting with benzene. The initial colorless band yielded triphenylphosphine selenide (0.100 g) admixed with a small amount of triphenylphosphine. A pale red band led to recovery of 2 (0.009 g). The subsequent dark band upon evaporation yielded a residue (0.079 g) which was crystallized from methanol–benzene to give dark brown 3 (0.069 g, 75%): mp 144–145°C; mass spectrum M^+ 628 (100%); NMR δ 3.83 s; λ_{max} (log ϵ) 212 nm (4.16), 260 (4.39), 285 (4.43), 328 sh (3.70), 422 (4.00).

Anal. Calcd for $C_{14}H_{12}O_8Se_4$: C, 26.94; H, 1.94. Found: C, 27.36; H, 2.01.

Tetraselenafulvalene (4). A mixture of 3 (0.100 g) and lithium bromide (0.216 g) in hexamethylphosphoramide (5 ml) was heated gradually to 80°C. There was gas evolution and considerable lightening of color. When the gas evolution ceased, the temperature was raised to 155–160° for 10 min by which time TLC indicated one spot corresponding to 4. The cooled mixture was diluted with water and extracted with cyclohexane containing 5% benzene. The orange organic extract was washed, dried (Na_2SO_4), and evaporated to yield salmon-pink plates (0.045 g), which were recrystallized from hot hexane to give pink plates (0.025 g, 35%) of TSeF (4), mp 134°C, identical in all respects (melting point, mass spectrum, uv spectrum, and TLC) with an authentic specimen of 4.[1] Low-temperature crystallization of 4 sometimes affords a labile crystalline modification (pale yellow needles) which reverts to the pink form on standing at room temperature in a hexane suspension.

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Registry No.—1, 17107-01-4; 2, 57653-12-0; 3, 57653-13-1; 4, 54489-01-9; dimethyl acetylenidicarboxylate, 762-42-5.

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An Improved Synthesis of 4-Ethylsulfonyl-1-naphthalenesulfonamide

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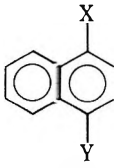
4-Ethylsulfonyl-1-naphthalenesulfonamide (1, ENS) has been reported[1] to promote experimental bladder carcinogenesis. ENS has previously been synthesized from 4-amino-1-naphthalenesulfonic acid in an unspecified yield by Brimelow and Vasey.[2] Turner and Dean[3] have reported that the method of Brimelow and Vasey gives low chemical yields and have described their own synthesis of ENS starting from 4-nitro-1-naphthylamine. In our hands, the method of Turner and Dean, which introduces both sulfur functions by diazonium salt reactions, has given an overall yield on the order of 10%. We report here a convenient high-yield, five-step synthesis of ENS which we believe to be superior to both other methods.

Conversion of commercially available 1-naphthalenethiol (2) to the ethylthioether 3 was accomplished by standard procedures.[4] Sulfonation of 3 using 1 equiv of chlorosulfonic acid gave the sulfonic acid 4 which was isolated as the sodium salt 5. The acid chloride 6 was prepared from 5 according to the method of Bossard et al.[5] Direct conversion of 3 to 6 by using 2 equiv of chlorosulfonic acid was attempted, but a dark-colored, heterogeneous product was obtained and the one-step conversion was deemed unsuitable. Treatment of 6 with ammonia gave the thioether sulfonamide 7 which was converted to ENS by peroxide oxidation. The ir spectrum of ENS synthesized by these reactions was identical with that of ENS prepared by the method of Turner and Dean.[3] This serves to establish that the sulfonation of 3 took place in the 4 position, since their starting material and products were known to have 1,4-substituent orientation. The overall conversion of 2 to 1 was typically 50–60%. Both 7 and ENS exhibited two different crystalline modifications: mp 128 or 141 °C for 7 and mp 184 or 198 °C for ENS. In both cases, crystallization from alcohol produced the higher melting forms in instances where the previously unreported lower melting forms were obtained as crude reaction products.



1, X = SO_2NH_2; Y = SO_2Et
2, X = H; Y = SH
3, X = H; Y = SEt
4, X = SO_3H Y = SEt
5, X = SO_3Na; Y = SEt
6, X = SO_2Cl; Y = SEt
7, X = SO_2NH_2; Y = SEt

Experimental Section

General. Melting points and boiling points are uncorrected. Anhydrous solvents were prepared by drying over molecular sieve. Infrared spectra were recorded on a Perkin-Elmer Model 710 spectrophotometer. Reactions were monitored and product purity checked by thin layer chromatography on precoated silica gel 60 F-254 plates (EM Laboratories) using toluene–ethyl acetate (1:1 v/v) as a developing solvent. The compounds and their approximate R_f values follow: 1 (0.47), 3 (0.91), 6 (0.91), 7 (0.64).

1-Ethylthionaphthalene (3). A mixture of 2 (26.44 g, 0.165 mol) and NaOH solution (2.5 N, 138 ml) was cooled in an ice bath. Diethyl sulfate (30.4 g, 0.197 mol) was added, and the mixture was stirred for 20 min. The ice bath was removed, and the mixture was refluxed for 1 h. A pale-yellow oil separated upon cooling. The reaction mixture was extracted with ether, and the organic layer was separated, washed with water, and dried over anhydrous $MgSO_4$. After the ether was removed (steam bath), the residue was fractionated through a 6-cm column packed with glass helices to give 3 as a colorless liquid (28.2 g, 91%), bp 98–105 °C (0.2 Torr) [reported[6] 175–176 °C (25 Torr)].

Sodium 4-Ethylthio-1-naphthalenesulfonate (5). A solution of 3 (14.1 g, 75 mmol) in anhydrous $CHCl_3$ (75 ml) was placed in a flask equipped with a magnetic stirrer, addition funnel, condenser, and drying tube and was cooled in an ice bath. A solution of chlorosulfonic acid (8.74 g, 75 mmol) in anhydrous $CHCl_3$ (150 ml) was added dropwise over a period of 1.5 h. A colorless solid began to precipitate from the reaction mixture after ca. two-thirds of the chlorosulfonic acid had been added. (In another reaction, this solid was filtered to give 4 as a colorless powder, mp 81–83 °C). After stirring for 0.5 h, the ice bath was removed, and stirring was continued for 1 h. Evaporation of the $CHCl_3$ under reduced pressure gave a colorless semisolid which was partitioned between ether (50 ml) and water (150 ml). The aqueous layer was separated, warmed to expel residual ether, and made basic by the addition of 50% NaOH solution (8 g), during which time a colorless precipitate formed. Saturated NaCl solution (100 ml) was added and the mixture cooled. The precipitate was filtered and washed sparingly with cold water to give 5 (18.4 g, 82%) as a colorless solid containing one-half of a water of hydration: ir (KBr) 3400 (OH), 1200 ($ArSO_3Na$), and 1070 cm^{-1} ($ArSO_3Na$).

Anal. Calcd for $C_{12}H_{11}S_2O_3Na \cdot \frac{1}{2}H_2O$: C, 48.15; H 4.00; Na, 7.68. Found: C, 48.38; H, 4.18; Na, 7.64.

4-Ethylthio-1-naphthalenesulfonyl Chloride (6). A mixture of 5 (2.90 g, 9.7 mmol) and anhydrous DMF (4 ml) was placed in a flask equipped with a magnetic stirrer, condenser, and drying tube and was cooled in an ice bath. Thionyl chloride (1.10 ml, 15 mmol) was added, and after 5 min the ice bath was removed and the mixture allowed to warm to room temperature. Stirring was continued for 2.5 h. Evaporation of the DMF under reduced pressure gave a yellow oil which was extracted with warm benzene (3 × 40 ml). After centrifugation to remove precipitated salt, the organic extracts were combined, washed with water (2 × 15 ml), and dried over anhydrous $MgSO_4$. Evaporation of the benzene under reduced pressure gave 6 (2.73 g, 98%, mp 78–80 °C) as a yellow solid which was sufficiently pure for the next reaction. Crystallization from acetonitrile gave 6 as yellow needles: mp 80–81 °C; ir (KBr) 1365 ($ArSO_2Cl$), 1195, 1165 ($ArSO_2Cl$), and 1145 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}S_2O_2Cl$: C, 50.26; H, 3.87, Found: C, 50.29; H, 4.00.

4-Ethylthio-1-naphthalenesulfonamide (7). A solution of 6 (1.43 g, 5 mmol) in anhydrous acetonitrile (20 ml) was placed in a flask equipped with a magnetic stirrer, gas inlet, and balloon and was cooled in an ice bath. Anhydrous ammonia was added through the gas inlet. A precipitate developed immediately in the reaction mixture. The mixture was stirred for 1 h with periodic additions of ammonia sufficient to keep the balloon slightly inflated. Water was added, and the acetonitrile was evaporated in a stream of air. Filtration of the precipitated solid gave 7 as colorless needles (1.25 g, 93%), mp 141–142 °C (reported[2] 141–142 °C). The material was sufficiently pure for conversion to ENS: ir (KBr) 3380 (NH), 3270 (NH), 1305 ($ArSO_2NH_2$), 1145 cm^{-1} ($ArSO_2NH_2$).

4-Ethylsulfonyl-1-naphthalenesulfonamide (1). A mixture of 7 (1.34 g, 5 mmol), HOAc (7.5 ml), and 30% H_2O_2 (5 ml, 37 mmol) was heated to 90 °C for 1 h. Water (75 ml) was added to the hot, pale-yellow solution, and the product separated as fine crystals. The mixture was cooled in ice, filtered, and washed with water to give 1 as colorless needles (1.37 g, 91%): mp 198–199 °C (reported[2,3] 198 °C); ir (KBr) 3345 (NH), 3250 (NH), 1335 ($ArSO_2R$), 1310 ($ArSO_2NH_2$), 1280, 1190, 1165 ($ArSO_2R$), 1145 ($ArSO_2NH_2$), and 1125 cm^{-1}.

Acknowledgment. This work was performed under the auspices of the U.S. Energy Research and Development Administration. We wish to thank Mrs. Ruby Ju, University of New Mexico, for performing the elemental analyses.

Registry No.—1, 842-00-2; 2, 529-36-2; 3, 17539-31-0; 4, 57559-91-8; 5, 57559-92-9; 6, 57559-93-0; 7, 28177-06-2; chlorosulfonic acid, 7790-94-5.

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Reinvestigation of the Acetylation of Thioanisole. Effect of the Mole Ratio of Aluminum Chloride

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In the chloromethylation of thioanisole with methylal and Lewis acids,[1] it was shown that the ratio of the products, *p*- and o-methylthiobenzyl chloride, could be controlled over a wide range by choice of the Lewis acid and the mole ratio in which it was used. The phenomenon was attributed to reaction of thioanisole as its Lewis acid complex.[2] The stronger the complex, the greater the para position specificity.

To my knowledge, this distinctive behavior of the methylthio substituent in electrophilic substutions has not previously been emphasized. An example of a different electrophilic reaction would lend credence to the idea which has, at the least, considerable synthetic value.

I now wish to report that when acetyl chloride is added to a solution of thioanisole and aluminum chloride in 1,2-dichloroethane (EDC), the yield and isomer ratio of the methylthioacetophenones are influenced by the molar ratio of the reactants. Table I gives some idea of the magnitude of the effect. Increasing the ratio of thioanisole from unity to 11:1 drops the yield from near quantitative to 40%. At the same time the ratio of *p*- to *o*-methylthioacetophenone decreases from 500:1 to 6:1. The order of addition was not a factor; mixing in all cases was at −10 to −20°C, and the reaction mixtures were worked up after 20–24 h at room temperature.[3]

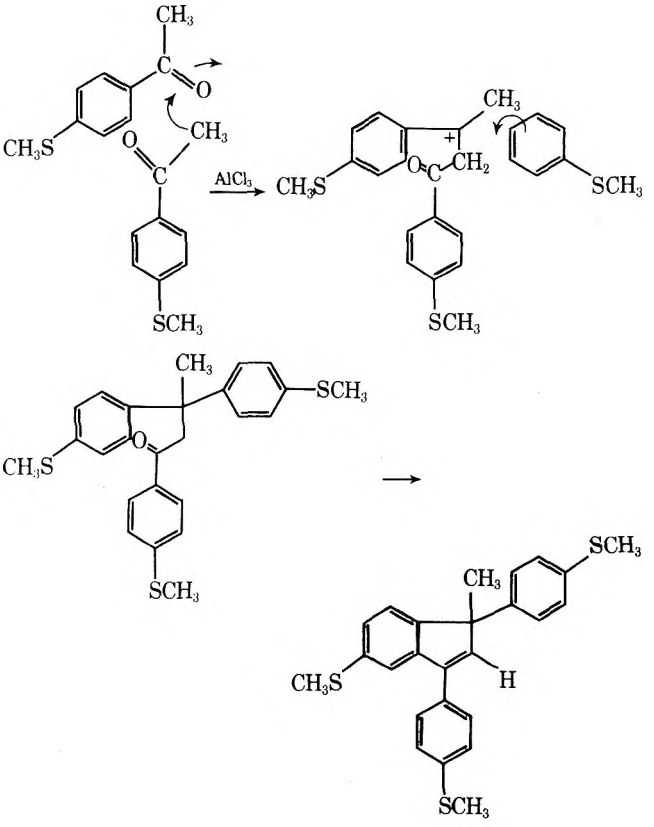
Table I. Acetylation[a] of Thioanisole at 22–24°C

Reaction	Mole ratio thioanisole: $AlCl_3$	Para/ortho ratio[b]	Yield, %[c]
1	1	99.8–0.2	95
2	2	98–2	95
3	5	95–5	80
4	11	86–14	40

[a] Acetyl chloride was equimolar with aluminum chloride. The amount of solvent EDC was changed slightly in order to maintain the same total reaction volume. Reaction 4 was run neat in the excess thioanisole. [b] From GC area percent measurements. No meta isomer was detected with three different GC and two different TLC systems. [c] Computed by GC internal standard method (heptadecane). Includes both isomers.

Reactivity of thioanisole is markedly retarded by excess $AlCl_3$. When 1 equiv of $AlCl_3$ was added for *each* reagent, the yield dropped to 14% without significant by-product formation.[4] When 1 equiv of 1:1 acetyl chloride–$AlCl_3$ complex was added to equimolar thioanisole, benzene, and aluminum chloride in EDC, approximately equal yields[5] of acetophenone and methylthioacetophenone were formed. Had the previously reported[6] K_{rel} thioanisole/benzene value of 7.2×10^3 applied, the benzene would have remained essentially unreacted.

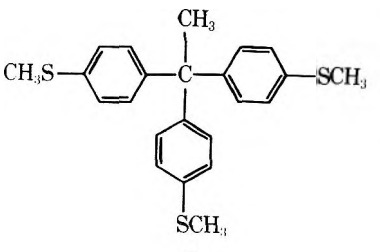
Two by-products of unusual structure were noted, especially in reactions which contained a large excess of uncomplexed thioanisole. The first one, fluorescent, was assigned the indene structure, 1, on the basis of a variety of spectral analyses and chemical plausibility. It probably arose by some variant of the scheme below.



1

In particular, 1 shows in the ^1H NMR ($CDCl_3$) three distinguishable *S*-methyls (δ 2.4), one C-methyl (δ 1.7), one vinylic proton (δ 6.4), and a complex pattern of 11 aromatic protons. Uv absorbance [log ε 4.57 (MeOH) at 277 nm] and mass spectrum (M^+ *m/e* 420) are supportive. The positions of *S*-methyl substitution are only presumed to be as shown.

The second compound may be assigned a structure on the basis of its much simpler NMR and molecular ion at *m/e* 396.



2

The aromatic AA'BB' pattern, single *S*-methyl resonance, and a *C*-methyl signal in the overall ratio of 4:3:1 can fit only the symmetrical **2**. Condensation of *p*-methylthioacetophenone with two molecules of an aromatic seems an unexceptional reaction; however, it does not appear to have been reported.

In summary, the type and extent of sulfur complexation in thioanisole, and presumably analogous compounds, with Lewis acids can markedly affect the rate and product of some electrophilic reactions.

Experimental Section[7]

Materials. Reagents and solvents were used as obtained from commercial suppliers.

Pure ***p*-methylthioacetophenone** was obtained from an acetylation in EDC which was run equimolar in aluminum chloride, acetyl chloride, and thioanisole. The pure material showed mp 82–83°C (heptane) (lit.[8] 79–80°C); NMR (CCl_4) δ 2.45 (s, 6, CH_3), 7.45 (m, 4, aromatic). The two methyl groups were resolved by the addition of a little pyridine. Mass spectrum *m/e* (rel intensity) 166 (M^+, 59), 151 (100), 123 (21), 108 (14).

Pure ***o*-methylthioacetophenone** was formed by reaction of methyllithium with *o*-methylthiobenzoic acid in ether. Crystals from hexane showed mp 44.5–46.5°C (lit.[9] mp 45–47°C). The NMR was as previously described.[5] Mass spectrum *m/e* (rel intensity) 166 (M^+, 33), 151 (100), 127 (7), 108 (10). While this compound was readily separated from its para isomer on the GC column used,[10] resolution by TLC on commercial silica gel plates with hexane–benzene mixtures was unsatisfactory.

Acetylation Experiments. A. Entry 1, Table I. Two milliliters (28.1 mmol) of acetyl chloride was added over 2–3 min to a cold (−10 to −20°C) solution of 28.4 mmol of $AlCl_3$ and 30 mmol of thioanisole in 33 ml of EDC with stirring in a nitrogen atmosphere. The reaction mixture was warmed to and stirred at room temperature for 20–24 h, then quenched on to ice and water and worked up conventionally. The dried ($MgSO_4$) solution was diluted to a standard volume with EDC for quantitation by GC. Experiment 2 used 56 mmol of thioanisole and 30 ml of EDC; 3 used 141 mmol of thioanisole and 20 ml of EDC; and 4 was run with 311 mmol of thioanisole as reactant and solvent. All other aspects of these experiments were identical with 1 above.

B. Excess $AlCl_3$. Reaction was similar to A above, except that the mixture of 60.5 mmol of $AlCl_3$ and 30 mmol of thioanisole in 32 ml of EDC was a slurry at first. After addition of 28.1 mmol of acetyl chloride, substantial solution occurred. Work-up as before gave a product solution which represented a 98:2 para:ortho isomer ratio in 14% overall yield. Thin layer chromatograms of the nonvolatile constituents showed no other appreciable products.

C. To cold (−10 to −20°C) solutions of 28.1 mmol of acetyl chloride and 28.4 mmol of aluminum chloride in 27 and 32 ml of EDC were added 84.5 and 42.2 mmol of thioanisole, respectively. After completion and work-up as in A, the isomer ratios were 98.8:1.2 and 99.5:0.5, respectively.

D. Competitive Acetylation. To 4 g (30 mmol) of aluminum chloride in 18 ml of EDC were added 2.22 g (28.5 mmol) of benzene and 3.49 g (28.1 mmol) of thioanisole below 0°C. The $AlCl_3$ dissolved. A solution of electrophile was prepared by adding 2.21 g (28.2 mmol) of acetyl chloride to a cold (0 to −10°C) stirred slurry of 3.8 g (28.5 mmol) of aluminum chloride in 12 ml of EDC. The latter solution was added to the former below −10°C, and the reaction allowed to continue as with the others. After the same work-up GC determination showed 48.6:51.4 area ratios of *p*-methylthioacetophenone to acetophenone, equivalent to 43:57 molar ratios. The para/ortho ratio of methylthioacetophenones was 96:4.

By-Product Isolation. A reaction similar to entry 4 (Table I) was freed of most of the excess thioanisole by distillation under high vacuum following the normal work-up. The residue was crystallized from hot heptane to give impure methylthioacetophenone and a mother liquor enriched in the impurities. Fractional crystallization of the mother liquor residue first with ether, then ethyl acetate and acetonitrile gave the pure 1,3-diaryl-1-methylindene **1**, mp 145.5–146.5°C, needles from CH_3CN. The NMR is described in the text, as is the uv absorption spectrum. Mass spectrum *m/e* (rel intensity) 420 (M^+, 100), 405 (15), 373 (30), 166 (13), 151 (47), 149 (33).

Anal. Calcd for $C_{25}H_{24}S_3$: C, 71.38; H, 5.97. Found: C, 71.39; H, 5.95.

The other component, **2**, a triarylethane, was obtained from the above ether crystallization almost pure. Recrystallization twice from acetonitrile gave single spot material: mp 142–144°C; NMR ($CDCl_3$) δ 2.13 (s, 3, CCH_3), 2.44 (s, 9, SCH_3), 7.12 (q, 12, aromatic); mass spectrum *m/e* (rel intensity) 396 (M^+, 40), 381 (100), 366 (4.5), 287 (4.8), 273 (8.9), 272 (14), 178 (5.7), 174 (6.7).

Anal. Calcd for $C_{23}H_{24}S_3$: C, 69.65; H, 6.1. Found: C, 69.13; H, 5.79.

A portion of another experiment was chromatographed on preparative layer SiO_2 plates with hexane–benzene to give a fraction consisting almost exclusively of **1** and **2**. Integration of the ^1H NMR spectrum showed 11 and 15% conversions to **1** and **2**, respectively, from acetyl chloride.

Registry No.—**1**, 57559-89-4; **2**, 57559-90-7; *p*-methylthioacetophenone, 1778-09-2; aluminum chloride, 7446-70-0; acetyl chloride, 75-36-5; thioanisole, 100-68-5; *o*-methylthioacetophenone, 1441-97-0; *o*-methylthiobenzoic acid, 3724-10-5.

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(5) See Experimental Section for details.
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(7) Melting points are uncorrected. Elemental analyses are by Mr. J. P. Gilbert and his associates of these laboratories. NMR spectra were obtained with a Jeolco C-60 HL or Hitachi Perkin-Elmer R-24A spectrometer. Mass spectra were obtained with an LKB 9000 spectrometer at 70 eV. For the sake of brevity, only portions of some spectra are reported.
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(10) 10 ft × 0.25 in. 3% Poly A-103 on 100/120 Gas Chrom Q.

Regioselectivity in the Cyclization of β,γ-Epoxy Carbanions. Application to the Total Synthesis of *trans*-Chrysanthemic Acid[1]

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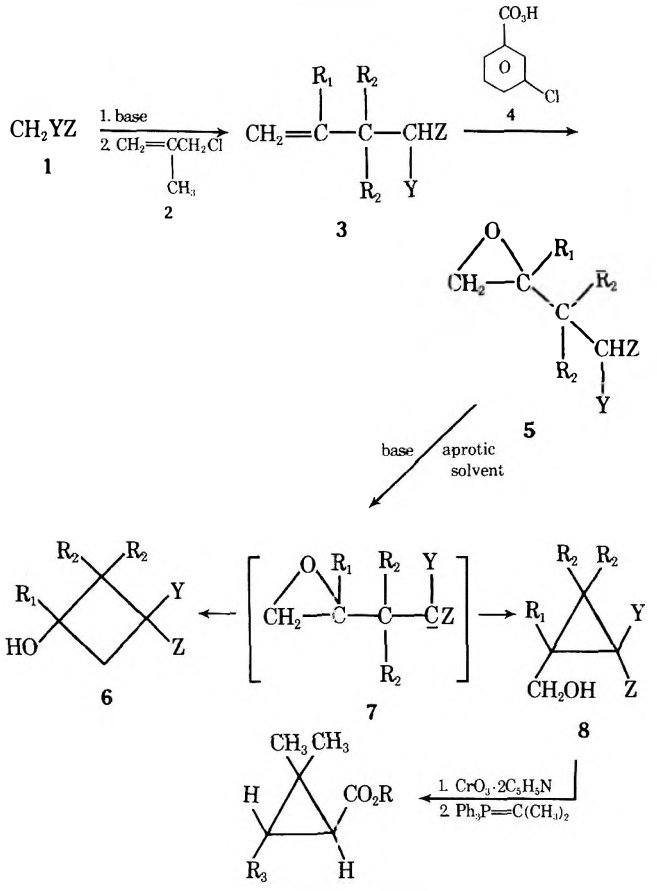
It is generally found that three- and five-membered carbocycles form considerably faster than four-membered rings in intramolecular displacement reactions.[2] A notable exception was recently reported[3] after a study of the regioselectivity in δ-epoxynitrile cyclizations involving SN2 type transition states. Such systems are unique in that, with equal substitution at both ends of the oxirane ring, cyclobutanes are always formed in preference to cyclopentanes. In view of the fact that previous reactions involving the base-promoted cyclization of the corresponding epoxy esters were generally carried out in protic solvents,[4] a study was undertaken to determine the site of attack in intramolecular alkylations undergone by β,γ- and γ,δ-epoxy carbanions in an aprotic solvent. The results of cyclizations undergone by a few representative β,γ-epoxy carbanions (**7**) are discussed in this note.

In two of the three systems (**5a,b**) examined, formation of a three-membered carbocycle requires substitution at a

tertiary carbon, whereas attack at the less hindered primary carbon would lead to a cyclobutanoid. In all systems examined, based on NMR and TLC analysis of the isolated reaction product, no evidence for formation of the four-membered carbocycle (**6**) was obtained.[5]

Epoxides **5a** and **5b** were prepared as outlined in Scheme I. Alkylation of diphenylmethane (**1a**) and ethyl phenylacetate (**1b**) with methallyl chloride (**2**) afforded the corresponding olefins (**3a,b**) in moderate yield. Subsequent treatment of the latter with *m*-chloroperbenzoic acid (**4**) afforded the corresponding epoxides (**5a,b**) in approximately 80% yield after purification via column chromatography. Base-promoted cyclization of these epoxides (**5a,b**) was achieved using anhydrous dimethyl sulfoxide as the solvent and sodium hydride to generate the intermediate anions (**7a,b**).

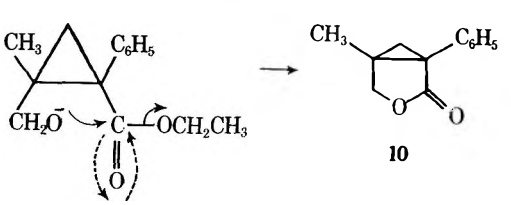
Scheme I



9d, R = CH_2CH_3; R_3 = CHO
e, R = CH_3; R_3 = CHO
f, R = H; $R_3 = (CH_3)_2C{=}CH$

a, R_2 = H; $R_1 = CH_3$; Y = Z = C_6H_5
b, R_2 = H; $R_1 = CH_3$; Y = C_6H_5; Z = $CO_2CH_2CH_3$
c, R_1 = Z = H; $R_2 = CH_3$; Y = $CO_2CH_2CH_3$

In one of the systems examined (**5b**), the only identifiable product after purification was a bicyclic lactone (**10**) whose formation from the intermediate cyclization product (**8b**) can be rationalized as shown below.



To illustrate the utility of this type of cyclization, a total synthesis of *trans*-chrysanthemic acid (**9f**),[6] many esters of which have insecticidal properties, has been achieved using the carbanion derived from an appropriately substituted epoxy ester (**5c**) as the key intermediate. The synthesis was effected as outlined in Scheme I. Ethyl 4,5-epoxy-3,3-dimethylpentanoate (**5c**) was prepared in 68% overall yield from 3-methyl-2-buten-1-ol[7] by a Claisen-type reaction[8] using triethyl orthoacetate, followed by epoxidation of the resulting unsaturated ester (**3c**) with *m*-chloroperbenzoic acid (**4**). Treatment of the resulting epoxy ester (**5c**) with 2 equiv of lithium diisopropylamide[9] and hexamethylphosphoramide in tetrahydrofuran at −70 °C afforded, after purification, only one identifiable product in 40% yield, cyclopropanoid **8c**. Since the sole isolated cyclization product obtained from epoxy ester **5b** was lactone **10** rather than the expected hydroxy ester **8b**, the absence of any lactone in the cyclization product obtained from epoxy ester **5c** indicates the trans stereochemistry of hydroxy ester **8c**. Further evidence was obtained by subsequent oxidation of the latter alcohol (**8c**) using chromium trioxide–pyridine complex in dichloromethane[10] to give in 90% yield the corresponding aldehyde (**9d**), whose NMR spectrum was compared to that previously reported[11] for methyl *trans*-2-formyl-3,3-dimethylcyclopropanecarboxylate (**9e**). Since the latter has been converted[11] to *trans*-chrysanthemic acid (**9f**), this step completes a formal total synthesis of this important terpenoid.

Experimental Section[12]

4,4-Diphenyl-2-methyl-1-butene (3a). Sodium metal (0.64 g, 27 mg-atoms) was added in small pieces to 60 ml of liquid ammonia to which had been added a small crystal of ferric nitrate. This mixture was stirred and refluxed (−33 °C) until the blue color had been discharged. After dropwise addition of a solution of 4.20 g (25 mmol) of diphenylmethane (**1a**) in 5 ml of anhydrous ether, the resulting deep red solution was stirred for an additional 30 min before 2.2 g (25 mmol) of methallyl chloride (**2**) in 5 ml of anhydrous ether was added dropwise over a period of 10 min. After the ammonia was allowed to evaporate slowly overnight, the mixture was partitioned between water and ether. Extraction with ether, followed by fractional distillation, afforded 2.38 g (43%) of olefin **3a**; bp 103–105 °C (0.40 mm) [lit.[13] bp 78–80 °C (0.01 mm)]; λ_{max} (film) 1655 (C=C), 1600, 1495, 890, 745, 695 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.33 (s, 10 aromatic H's), 4.75 (broad s, C=CH_2), 4.23 (t, J = 8 Hz, CH_2CH), 2.80 (d, J = 8 Hz, CH_2CH), 1.67 ppm (s, vinyl CH_3).

4,4-Diphenyl-2-methyl-1,2-epoxybutane (5a). A mixture of 2.22 g (10 mmol) of olefin **3a** and 2.10 g of 85% *m*-chloroperbenzoic acid (**4**)[7] in 50 ml of methylene chloride was refluxed for 15 h. After cooling this solution, it was washed twice with 1 M aqueous sodium hydroxide, and the crude product was isolated in the usual manner.[12] Chromatography on Florisil (elution with 5% ether–hexane) afforded 1.85 g (78%) of epoxide **5a**: λ_{max} (film) 1660, 1600, 1070, 1035, 810, 750, 705 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.35 (10 aromatic H's), 2.20 (s, CH_2O), 1.17 ppm (s, CH_3). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.41; H, 7.60.

(2,2-Diphenyl-1-methylcyclopropyl)methanol (8a). Epoxide **5a** (1.19 g, 5.0 mmol) in 10 ml of dimethyl sulfoxide was added dropwise over a period of 15 min to a vigorously stirred mixture of 6.0 mmol of sodium hydride in 40 ml of dimethyl sulfoxide. After this mixture was stirred at room temperature for 15 h, it was poured into 200 ml of H_2O and acidified with dilute hydrochloric acid, and the product was isolated by extraction with ether. Recrystallization of the crude product from 5% ether–hexane afforded 0.69 g (58%) of solid alcohol **8a**: mp 104–105 °C; λ_{max}(KBr) 3250 (OH), 1010, 770, 740, 695 cm^{-1}; δ_{Me_4Si}(CCl_4) 3.46 (s, CH_2OH), 1.57 (s, OH), 1.28 (AB quartet, peaks at 1.43, 1.35, 1.21, 1.13, 2 cyclopropyl H's), 1.11 ppm (s, CH_3). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.45; H, 7.77.

Ethyl 2-Phenyl-4-methyl-4-pentenoate (3b). A solution of 1.64 g (10 mmol) of ethyl phenylacetate (**1b**) in 10 ml of dimethyl sulfoxide was added dropwise to a vigorously stirred mixture of 12 mmol of sodium hydride in 50 ml of dimethyl sulfoxide. After evolution of hydrogen had ceased, a solution of 0.91 g (10 mmol) of methallyl chloride (**2**) in 10 ml of dimethyl sulfoxide was added

slowly. This mixture was subsequently stirred at room temperature for 2 h, after which it was diluted with 400 ml of water and the product was isolated by extraction with ether. Evaporative distillation afforded 1.34 g (62%) of unsaturated ester **3b**: bp 78–82 °C (bath temperature, 0.1 mm) [lit.[11] bp 136–138 °C (16 mm)]; λ_{max} (film) 1735 (C=O), 1650 (C=C), 1605, 1500, 1165, 1035, 900, 740, 700 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.41 (s, 5 aromatic H's), 4.82 (broad s, CH_2=C), 4.15 (quartet, J = 7 Hz, OCH_2CH_3), 1.73 (s, vinyl CH_3), 1.16 ppm (t, J = 7 Hz, OCH_2CH_3)

Ethyl 2-Phenyl-4-methyl-4,5-epoxypentanoate (5b). Using the procedure described above for the preparation of **5a**, epoxide **5b** was obtained in 74% yield as a colorless oil: λ_{max} (film) 1730 (C=O), 1160, 1030, 700 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.43 (s, 5 aromatic H's), 4.19 (quartet, J = 7 Hz, OCH_2CH_3), 1.28 (s, CH_3), 1.17 ppm (t, J = 7 Hz, OCH_2CH_3). Since this oily epoxide (**5b**) proved in our hands to be unstable to vacuum distillation, no attempt was made to further purify it.

1-Phenyl-2-oxo-5-methyl-3-oxabicyclo[3.1.0]hexane (10). Treatment of 0.600 g (2.56 mmol) of crude epoxide **5b** with 3.1 mmol of sodium hydride in 50 ml of anhydrous dimethyl sulfoxide using the procedure described above for the preparation of alcohol **8a** afforded, after chromatography on Florisil and recrystallization from 10% ether–hexane, 160 mg (34%) of bicyclic lactone **10**: mp 63–64 °C; λ_{max} (KBr) 1765 (C=O), 1165, 1075, 1010, 755, 695 cm^{-1}; δ_{Me_4Si} (CCl_4) 7.54 (s, C_6H_5), 4.41 (AB quartet, peaks at 4.60, 4.45, 4.37, 4.22, CH_2O), 1.54 (AB quartet, peaks at 1.70, 1.62, 1.45, 1.37, 2 cyclopropyl H's), 1.09 ppm (s, CH_3). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.56; H, 6.43. Found: C, 76.65; H, 6.64.

Ethyl 3,3-Dimethyl-4-pentenoate (3c). A mixture of 1.718 g (19.94 mmol) of 3-methyl-2-buten-1-ol,[7] 26 ml of triethyl orthoacetate,[7] and 74 mg (1 mmol) of propionic acid was heated at 140° for 36 h under conditions that allowed distillative removal of ethanol through a Vigreux column. After cooling this solution, it was poured into 40 ml of 5% (v/v) aqueous sulfuric acid and this mixture was subsequently stirred (with cooling in a water bath to maintain the temperature at or below 25 °C) for 5 min to hydrolyze the excess triethyl orthoacetate. Extraction of the crude product with pentane, followed by chromatography on Florisil (elution with hexane–5% ether), afforded 2.204 g (71%) of ester **3c**: bp 35–45 °C (bath temperature, 0.10 mm); λ_{max} (film) 3120, 1735 (C=O), 1635 (C=C), 1230, 1200, 1120, 1025, 905 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.17–4.77 (complex pattern, 3 vinyl H's, peaks at 6.17, 5.99, 5.86, 5.69, 5.10, 5.08, 5.00, 4.97, 4.81, 4.79, and 4.77), 4.08 (quartet, J = 7.0 Hz, OCH_2CH_3), 2.21 (s, CH_2C=O), 1.22 (triplet, J = 7.0 Hz, OCH_2CH_3), 1.13 ppm (s, CH_3CCH_3). Anal. Calcd for $C_9H_{16}O_2$: C, 69.21; H, 10.33. Found: C, 69.03; H, 10.29.

Ethyl 4,5-Epoxy-3,3-dimethylpentanoate (5c). A solution containing 1.214 g (7.78 mmol) of unsaturated ester **3c** and 10 mmol of *m*-chloroperbenzoic acid[7] in 20 ml of anhydrous ether was refluxed for 18 h. After washing the ether layer with 5% aqueous sodium hydroxide and saturated brine, epoxide **5c** was isolated in the usual manner[12] in 95% yield bp 45–55 °C (bath temperature, 0.10 mm); λ_{max} (film) 1730 (C=O), 1260, 1230, 1115, 1030 cm^{-1}; δ_{Me_4Si} (CCl_4) 4.12 (quartet, J = 7.0 Hz, OCH_2CH_3), 2.80 (triplet, J = 3.5 Hz, oxirane CH), 2.54 (d, J = 3.5 Hz, oxirane CH_2), 2.23 (s, CH_2C=O), 1.26 (t, J = 7.0 Hz, OCH_2CH_3), 1.0 (s, CH_3), 0.97 ppm (s, CH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.78; H, 9.37. Found: C, 62.66; H, 9.36.

Ethyl 2-Hydroxymethyl-3,3-dimethylcyclopropanecarboxylate (8c). A solution of 944 mg (5.49 mmol) of ester **5c** and 2.0 ml of hexamethylphosphoramide in 10 ml of anhydrous tetrahydrofuran was added dropwise to a solution of 11 mmol of lithium diisopropylamide[9] in 50 ml of anhydrous tetrahydrofuran at −70 °C. After stirring this mixture at −70 °C for 7 h, the reaction was quenched by pouring the solution into 50 ml of saturated aqueous ammonium chloride solution. Extraction of the crude product with ether, followed by chromatography on Florisil (elution with 1:1 ether–hexane), afforded 378 mg (40%) of cyclopropanoid **8c**: bp 60–80 °C (bath temperature, 0.20 mm); λ_{max} (film) 3470 (OH), 1722 (C=O), 1205, 1170, 1110, 1025 cm^{-1}; δ_{Me_4Si} (CCl_4) 4.08 (quartet, J = 7 Hz, OCH_2CH_3), 3.57 (d, variable broadening, CH_2OH), 1.25 (t, J = 7 Hz, OCH_2CH_3), 1.21 ppm (s, 2 CH_3's). Anal. Calcd for $C_9H_{16}O_3$: C, 62.78; H, 9.37. Found: C, 62.59; H, 9.47.

Ethyl *trans*-2-Formyl-3,3-dimethylcyclopropanecarboxylate (9d). Oxidation of alcohol **8c** was effected using the method developed by Ratcliffe and Rodehorst,[10] affording the corresponding aldehyde (**9d**) in 90% yield bp 50–63 °C (bath temperature, 0.08 mm); >94% pure by VPC analysis,[15] oven temperature 155 °C, retention time 3.0 min; λ_{max} (film) 2775 (CHO), 1725 (ester C=O), 1700 (HC=O), 1225, 1170, 1100 cm^{-1}; δ_{Me_4Si} (CCl_4) 9.60 (d, J = 2.0 Hz, CHO), 4.12 (quartet, J = 7.0 Hz, OCH_2CH_3), 2.39 (d, J = 2.0 Hz, CHCHO), 2.37 (s, $CHCO_2CH_2CH_3$), 1.35 (s, CH_3), 1.30 (s, CH_3), 1.27 ppm (t, J = 7.0 Hz, OCH_2CH_3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.23; H, 8.50.

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Registry No.—**1a**, 101-81-5; **1b**, 101-97-3; **1c**, 79-09-4; **2**, 563-47-3; **3a**, 33925-52-9; **3b**, 14815-83-9; **3c**, 7796-72-7; **5a**, 54949-91-6; **5b**, 57496-91-0; **5c**, 57496-92-1; **8a**, 27067-50-1; **8c**, 40427-26-7; **9d**, 38692-37-4; **9f**, 827-90-7; **15**, 57496-93-2; 3-methyl-2-buten-1-ol, 556-82-1.

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Efficient Syntheses of Barrelene and Nenitzescu's Hydrocarbon[1]

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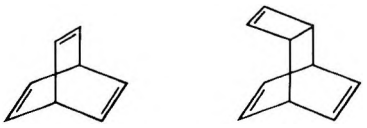
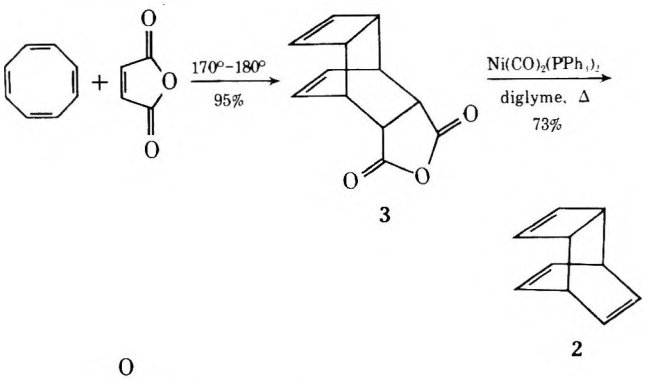
Since their initial syntheses, the hydrocarbons barrelene (bicyclo[2.2.2]octa-2,5,7-triene, **1**)[2,3] and Nenitzescu's hydrocarbon (tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene, **2**)[4,5] have been of interest since they are of theoretical interest, themselves, and since they offered ready access to some $(CH)_8$ and $(CH)_{10}$ hydrocarbons, respectively.[6] The studies related to **1** and **2** have been hampered owing to the inaccessibility of sizable quantities of the hydrocarbons. For example, the syntheses of barrelene were accomplished in less than



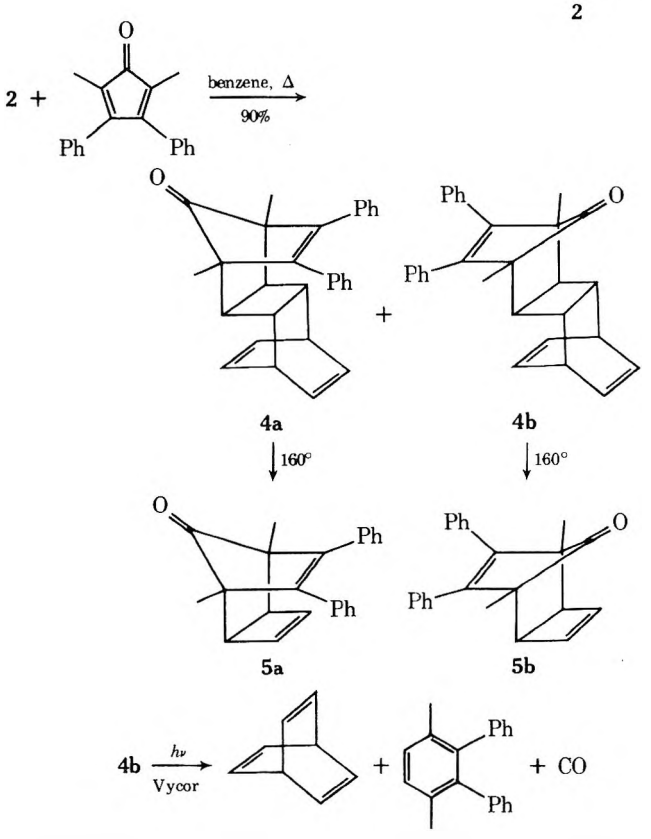
1 2

2% overall yield[2,3] and the early preparations of Nenitzescu's hydrocarbon suffered from a low yield in the final lead tetraacetate oxidative bisdecarboxylation step[4] or in the ability to scale up other oxidative bisdecarboxylation reaction sequences.[5]

Recently, the synthesis of **2** was accomplished via a six-step sequence in an overall yield from cyclooctatetraene of 36%.[7] The syntheses of related compounds in the laboratory using a [4 + 2] cycloreversion reaction to transfer a four-carbon unit from one moiety to another[8] led us to examine again the synthesis of **1** and **2** by a more efficient method. Using a related two-carbon transfer reaction (1,2-photoaromatization)[9] the latter compound could serve as a precursor of **1**.



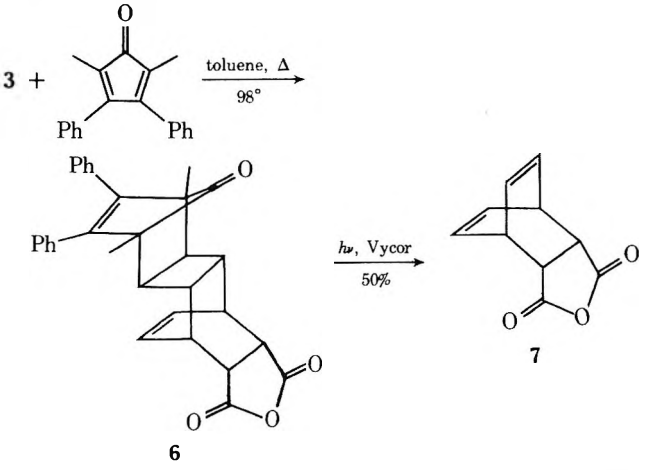
3 2



4a 4b 5a 5b

The Diels–Alder adduct **3**, prepared in 95% yield by allowing cyclooctatetraene and maleic anhydride to react at 170–180°, was oxidatively bisdecarboxylated with dicarbonylbis(triphenylphosphine)nickel[10] in refluxing diglyme to give tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (**2**) in 73% yield on a 20–25-g scale.[11] The overall yield for this two-step preparation from cyclooctatetraene was 69%.

The [4 + 2] cycloaddition reaction between **2** and 2,5-dimethyl-3,4-diphenylcyclopentadienone was accomplished in refluxing benzene and gave in 90% yield a mixture of endo and exo isomers **4a** and **4b**; the exo isomer was the predominant product and could be obtained pure in 70% yield. Upon heating to 160°, this pure isomer **4b** yielded the known exo ketone **5b** in 90% yield. The exo isomer **4b** upon ultraviolet irradiation (Vycor filter) in dry tetrahydrofuran, after vacuum transfer, gave a solution of barrelene (**1**), contaminated with a trace of benzene and cyclooctatetraene;[12] the yield of barrelene was 50%. As in all the earlier preparations, pure hydrocarbon was obtained by preparative gas chromatography. The yield of barrelene from cyclooctatetraene was 24%.



6 7

Other obvious variations in the reaction sequence were investigated. For example, the Diels–Alder reaction between anhydride **3** and the dienone proceeded in near quantitative yield to give **6**. This adduct upon 1,2 photoaromatization gave **7** in 50% yield. This "benzene Diels–Alder" product, **7**, is a crystalline solid and is stable in the cold. In solution the product slowly undergoes a retro-Diels–Alder reaction ($t_{1/2}^{25°}$ ~30 h) to yield benzene and maleic anhydride. Alternatively, when the adduct **6** was subjected to electrolytic oxidative bisdecarboxylation, the diene **4b** was obtained in only 33% yield. The thermal process using dicarbonylbis(triphenylphosphine)nickel could not be used, since as discussed above, the first formed product **4b** was thermally unstable under the reaction conditions.

Experimental Section

Unless otherwise noted, the following general conditions were used in all reactions. Infrared spectra were recorded using either a Perkin-Elmer 137 Infracord or a 237 grating spectrometer. NMR spectra were obtained with a Varian T-60 spectrometer and tetramethylsilane as an internal standard. Mass spectral analyses and elemental analyses were obtained from The Analytical Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (2). In a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer were placed *endo*-tricyclo[4.2.2.0^{2,5}]deca-3,5-diene-7,8-dicarboxylic anhydride (**3**, 22.5 g, 0.11 mol),[13] dicarbonyl bis(triphenylphosphine)nickel (87 g, 0.14 mol),[14] and anhydrous diglyme (200 ml). The solution was heated under vigorous reflux (bath temperature 200°, nitrogen atmosphere) for 3.5 hr, during which time the color of the solution changed from yellow-green to dark black.[15] The reaction was cooled to room temperature (some unreacted nickel catalyst precipitated), the condenser was replaced by a distillation head, and the diglyme and hydrocarbons were distilled under aspirator vacuum (bp 60–65°) into a dry ice cooled trap. An additional 50 ml of diglyme was added to the residue and distilled. The combined distillate was poured into water (1000 ml) and the mixture extracted with three 150-ml portions of isopentane. The hydrocarbon phase was washed three times with water (the complete removal of the diglyme established by GC analysis) and the isopen-

tane solution dried (Na_2SO_4). The solvent was distilled at atmospheric pressure using a 12-cm vacuum-jacket spiral wire filled column. The residue was distilled through a short-path still, bp 72–73° (18 mm), to yield 10.55 g (73%) of 98% (GC) pure hydrocarbon. The product displayed spectral characteristics identical with the reported values.[4,5]

***exo*-4,7-Dimethyl-5,6-diphenylpentacyclo[8.2.2.1^{4,7}.0^{2,9}.0^{3,8}]-pentadeca-5,11,13-trien-15-one (4b).** In a 250-ml, round-bottomed flask equipped with a reflux condenser were placed tricyclo-[4.2.2.0^{2,5}]deca-3,7,9-triene (**2**, 10.15 g, 0.078 mol), 2,5-dimethyl-3,4-diphenylcyclopentadienone dimer (20.0 g, 0.04 mol),[14] and dry benzene (100 ml). The solution was refluxed with magnetic stirring under a nitrogen atmosphere until the red color disappeared (~40 h) and cooled to room temperature, and ether (75 ml) was added. The white precipitate was filtered, washed with cold ether, and dried under reduced pressure at 25° to yield 21.1 g (70%) of exo isomer **4b**. An analytical sample was recrystallized from CCl_4–MeOH: mp 182–184° dec; NMR ($CDCl_3$) δ 1.19 (s, 6), 1.72–1.93 (m, 4), 3.62 (m, 2), 6.26–6.58 (overlapping triplets, apparent quintet, 4, J = 4 Hz), 6.78–7.30 (m, 10); ir (KBr) 696, 722, 760, 781, 809, 1395, 1440, 1755, and 2930 cm^{-1}; mass spectrum m/e 390 (M^+), 362 (M^+ − CO), 284 (M^+ − CO − benzene), 258.

Anal. Calcd for $C_{29}H_{26}O$: C, 88.19; H, 6.71. Found: C, 88.96; H, 6.76.

The filtrate was concentrated to a viscous oil, which was dissolved in hot CCl_4 (25 ml), and diluted with hot absolute EtOH (100 ml). The solution was rotary evaporated to 60 ml, the precipitate filtered, and the solid washed with EtOH. The filtrate was further concentrated to yield a product of lesser purity. A total of 7.1 g (22%) of product was obtained from the ethanolic solution, and these crops were enriched in the endo isomer: NMR ($CDCl_3$) δ 1.34 (s, 6), 1.88–2.30 (m, 4), 3.50–3.94 (m, 2), 6.25 (t, 2, J = 3.5 Hz), 6.51 (t, 2, J = 3.5 Hz), 6.85–7.32 (m, 10).

Bicyclo[2.2.2]octa-2,5,7-triene (1). To a quartz irradiation well equipped with a magnetic stirrer and a dry ice condenser was added a solution of **4b** (7.80 g, 20 mmol) in dry tetrahydrofuran (125 ml) and the solution was purged with dry nitrogen for 1 h. The solution was irradiated through a Vycor filter with a Hanovia 450-W lamp and the progress of the reaction followed by TLC (10% EtOAc–90% ligroin). After a 6-h period only traces of starting material remained and the irradiation was terminated. The reaction solution was transferred to a 250-ml, round-bottomed flask, the solution freeze–thaw degassed (five cycles, 25 μ), and the volatile material vacuum transferred to a 250-ml, round-bottomed flask cooled in liquid nitrogen; a thick yellow residue remained in the distillation flask. An additional 20 ml of tetrahydrofuran was added to the residue, and the vacuum transfer repeated. The combined tetrahydrofuran solution was concentrated by distillation through a 40-cm spinning-band column at atmospheric pressure to leave 7.26 g of solution (10.7 mol % barrelene by NMR analysis, yield 1.07 g, 51%) which contained benzene and cyclooctatetraene as trace contaminants. Pure barrelene was isolated by preparative gas chromatography (15 ft × 0.25 in., 2.5% SE-30, 120°) and a neat sample displayed spectral properties identical with the literature values.[2,3]

***exo*-1,6-Dimethyl-7,8-diphenyltricyclo[4.2.1.0^{2,5}]nona-3,7-dien-9-one (5b).** A sublimer containing **4a** (100 mg, 0.256 mmol) was heated at 160° under aspirator vacuum for 2 h. The white sublimate was collected, yield 70 mg (87%) of **5b**, and was resublimed under identical conditions: mp 132–135°;[16] NMR (CCl_4) δ 1.19 (s, 6), 3.09 (s, 2), 6.52 (s, 2), 6.88–7.32 (m, 10);[17] ir (CCl_4) 699, 848, 891, 907, 928, 970, 1010, 1070, 1170, 1185, 1280, 1370, 1445, 1485, 1770, 2900, and 3000 cm^{-1}; mass spectrum m/e 312 (M^+), 286 (M^+ − C_2H_2), 284, (M^+ − CO, base peak), 258.

Anal. Calcd for $C_{23}H_{20}O$: C, 88.43; H, 6.45. Found: C, 88.37; H, 6.29.

***exo*-4,7-Dimethyl-5,6-diphenylpentacyclo[8.2.2.1^{4,7}.0^{2,9}.0^{3,8}]-pentadeca-5,13-dien-15-onedicarboxylic Acid Anhydride (6).** A suspension of crude *endo*-tricyclo[4.2.2.0^{2,5}]deca-3,9-diene-7,8-dicarboxylic acid anhydride (12.2 g, 0.06 mol), 2,5-dimethyl-3,4-diphenylcyclopentadienone dimer (15.7 g, 0.03 mol), and 100 ml of toluene was heated under reflux for 24 h; the bright red color of the monomeric dienone gradually disappeared. The suspension was cooled in an ice bath, and the product filtered. To the filtrate there was added 100 ml of ether and a second crop of crystals was obtained. The combined crops were dried under vacuum: yield 27.6 g (98%); mp 278–280°; NMR ($CDCl_3$) δ 1.20 (s, 6), 2.02 (broad s, 4), 3.01 (t, 2, J = 2 Hz), 3.35 (m, 2), 6.45 (t, 2, J = 4 Hz), 6.80–7.30 (m, 10); ir (KBr) 750, 809, 915, 1085, 1220, 1770, and 1850 cm^{-1}; mass spectrum m/e 462 (M^+), 434 (M^+ − CO), 258.

Anal. Calcd for $C_{31}H_{26}O_4$: C, 80.50; H, 5.67. Found: C, 80.71; H, 5.48.

Bicyclo[2.2.2]octa-2,5-diene-7,8-dicarboxylic Anhydride (7). A solution of **6** (924 mg, 2 mmol) in dry tetrahydrofuran (30 ml) was placed in a Vycor tube fitted with a stopcock, the tube was cooled in ice water in a transparent quartz Dewar flask, and the solution was degassed with nitrogen. At ice temperature, the solution was irradiated for 9 h in a Rayonet reactor using 254-nm light sources. A small amount of solid material was filtered, and the solution treated twice with small portions of ligroin and the resulting solids removed. Finally, a 25-ml portion of ligroin was added and the flocculent precipitate filtered and dried (0°, vacuum) to give 190 mg (54%) of material of about 90% purity (NMR analysis): mp 70–80° dec; NMR ($CDCl_3$) δ 3.20 (t, 2, J = 1.5 Hz), 4.12 (m, 2), 6.54 (t, 2, J = 3.5 Hz); ir ($CHCl_3$) 824, 914, 930, 960, 1010, 1080, 1230, 1295, 1345, 1775, 1845, 2920, and 3020 cm^{-1}.

A small amount of **7** was recrystallized by dissolving it in a minimal amount of tetrahydrofuran at room temperature, followed by the addition of 4 volumes of ether. The resulting solution was chilled for 12 h and the crystalline precipitate was filtered (~30% recovery), mp 70–80% (dependent upon heating rate).

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.14; H, 4.83.

Registry No.—**1**, 500-24-3; **2**, 21604-76-2; **3**, 51447-09-7; **4a**, 57496-75-0; **4b**, 57526-53-1; **5b**, 30450-25-0; **6**, 57496-76-1; **7**, 57496-77-2; 2,5-dimethyl-3,4-diphenylcyclopentadienone, 26307-17-5.

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Oxidation of Secondary Alcohols with Ozone[1]

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The ozonation of alcohols has received only scattered attention throughout the literature.[2] Primary interest has been a mechanistic interpretation of the oxidation process. However, since we[1,3] and others[2] have noted fairly rapid

Table I

Alcohol	Registry no.	% ketone yield	Alcohol	Registry no.	% ketone yield
2-Propanol	67-63-0	83	2-Nonanol	628-99-9	57
2-Butanol	78-92-2	72	4-Nonanol	5932-79-6	68
2-Pentanol	6032-29-7	69	4-Decanol	2051-31-2	71
3-Pentanol	584-02-1	81	5-Decanol	5205-34-5	65
2-Hexanol	626-93-7	66	2,4-Dimethyl-3-pentanol	600-36-2	83
3-Hexanol	623-37-0	74	Cyclopentanol	96-41-3	53
2-Heptanol	543-49-7	62	Cyclohexanol	108-93-0	65
3-Heptanol	589-82-2	82	Cycloheptanol	502-41-0	74
4-Heptanol	589-55-9	70	Cycloheptanol		65[4]
2-Octanol	123-96-6	71	Cyclooctanol	696-71-9	69
4-Octanol	589-62-8	66	Cyclododecanol	1724-39-6	61

and complete conversion of alcohols to ketones upon ozonation, it was decided that a potentially useful synthetic oxidation method had presented itself. We tested the general applicability of this method by ozonizing 21 acyclic and cyclic secondary alcohols in methylene chloride at 0 °C.

Results and Discussion

Yield data for these oxidations are summarized in Table I.

The results indicate that ozonation gives ketone yields quite comparable to other oxidation methods.[5] Moreover VPC and ir analysis showed no residual alcohol in the raw product mixtures, whereas the more common oxidation processes frequently leave some unreacted alcohol.[6] Under the stated ozone flow conditions complete oxidation of 10–20 mmol of alcohol required 40–60 min at 0 °C.[7] The ketone products were essentially inert to "overozonation".[8]

As noted previously,[2,3] ozonation of alcohols, and most other functional groups, causes a certain amount of carbon–carbon scission. Likewise the present study showed minor yields of mono- and dibasic acids from the acyclic and cyclic alcohols, respectively. The nonvolatile acids were conveniently removed by either an aqueous bicarbonate wash or flash distillation prior to analysis. No other product impurities could be detected.[9]

The general utility of alcohol oxidation via ozonation is, of course, somewhat limited. Since the oxidation rate of alcohols is clearly many times slower than the addition of ozone to a carbon–carbon π bond,[2,3] the use of alkenols or alkynols is ruled out. The presence of other ozone reactive functional groups, e.g., aldehydes, amines,[10] etc., is also excluded. Finally, the rather slow rate of alcohol oxidation itself,[2] coupled with the necessity of ozonating at pressures close to atmospheric, appear to make large-scale oxidations impractical.[4]

However, ozonation, as an oxidation method, does offer some attractive advantages when compared to existing procedures. On a small preparative scale the alcohol is gently converted to ketone in a neutral organic medium[11] at a relatively low temperature. The side reactions which sometime accompany highly acidic or basic media and/or high temperatures are therefore eliminated. The work-up following ozonation is obviously quite simple, involving only simultaneous ozone quenching and carboxylic acid removal with an aqueous basic iodide wash.[9,12] Distillation to remove unreacted alcohol is unnecessary. Finally, the cost of the oxidizing agent itself, excluding the ozonator,[13] is minuscule when compared to that for most of the common oxidants.

Experimental Section

Welsbach T-408 and Airox C2P-9C ozonators were used to generate 3–5% O_3–O_2 mixtures at rates of 15–70 mmol of O_3 per hour. Rate of ozone flow was calculated by the standard iodide–thiosulfate method.[14]

Ozonations were generally carried out at 0 °C in a 100-ml three-necked flask with 1–2 g (10–20 mmol) of alcohol as a 1–2% w/v solution in CH_2Cl_2. The reaction solution also contained 10–20 mmol of nitromethane as an internal VPC standard. The reaction vessel was fitted with an inlet tube, magnetic stirrer, and a dry ice reflux condenser in series with an aqueous KI trap.

After ca. 45 min of ozonation, the reaction solution was washed with 20 ml of a 1 M aqueous KI–$NaHCO_3$ solution. The organic phase was dried with $MgSO_4$ and analyzed by VPC on 10 ft × 0.25 in. 10% SE-30, 20% DEGS, and 10% Carbowax columns. Identification of ketone products was accomplished by both comparing the peak retention times with those of the known ketones and by VPC collection and subsequent ir analysis of each peak.[15] Yields were calculated by using the VPC integration data coupled with the detector sensitivity calibration curves for each nitromethane–ketone mixture.

Registry No.—Ozone, 10028-15-6; 2-propanone, 67-64-1; 2-butanone, 78-93-3; 2-pentanone, 107-87-9; 3-pentanone, 96-22-0; 2-hexanone, 591-78-6; 3-hexanone, 589-38-8; 2-heptanone, 110-43-0; 3-heptanone, 106-35-4; 4-heptanone, 123-19-3; 2-octanone, 111-13-7; 4-octanone, 589-63-9; 2-nonanone, 821-55-6; 4-nonanone, 4485-09-0; 4-decanone, 624-16-8; 5-decanone, 820-29-1; 2,4-dimethyl-3-pentanone, 565-80-0; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7.

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(1) This research was supported by the National Science Foundation, Grant GP-18317, and the University of Montana Foundation. A preliminary report of this work was presented at the 30th Annual NWRACS Meeting, Honolulu, Hawaii, June 1975.

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(4) This yield of ketone was obtained from the oxidation of 20 g (0.18 mol) of alcohol. Complete disappearance of cycloheptanol required a 4-h reaction time.

(5) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Wiley-Interscience, New York, N.Y., 1971, pp 386–396.

(6) For example, we have found that the two-phase Jones oxidation procedure [H. C. Brown, C. P. Garg, and K. Liu, *J. Org. Chem.*, **36**, 387 (1971)] commonly leaves 3–6% unreacted alcohol.

(7) Oxidation was faster at higher temperatures, but was accompanied by an increase in the percentage of carbon–carbon scission. We are currently investigating Whiting's findings (ref 2) that a catalytic amount of sodium borohydride or sodium acetate reduces this unwanted side reaction.

(8) At 0 °C the oxidation cleavage of ketones is five to ten times slower than alcohol oxidation.

(9) Since the by-products of the reaction are O_2 H_2O, and a small amount of RCOOH (see Whiting et al., ref 2), samples of the product mixture were analyzed by VPC after shaking either with a solid KI–NaS_2O_3 mixture or with aqueous KI–$NaHCO_3$.

(10) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

(11) Oxidations were also carried out in CCl_4, $CHCl_3$, and $(CH_3)_2CO$. All solvents gave identical products and similar reaction rates.

(12) Alternatively, excess O_3 can be conveniently removed by purging the solution with N_2.

(13) The appearance of a number of relatively inexpensive air-cooled ozon-

ators on the market, coupled with the expanding investigation of O_3 water purification, has made ozonation available to most laboratories.

(14) See, for example, E. P. Parry and D. H. Hern, *Environ. Sci. Technol.*, **7**, 65 (1973).

(15) Ir spectra of the VPC collected ketones agreed closely with those from the literature. Sources: C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1970; "Sadtler Standard Spectra", Sadtler Research Laboratories, Philadelphia, Pa.

Isolation and Identification of β-Citraurol, a C_{30} Carotenoid in Citrus[1]

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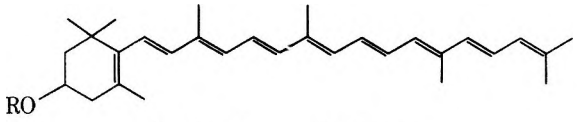
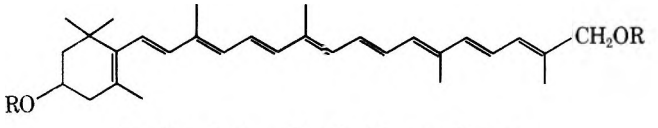
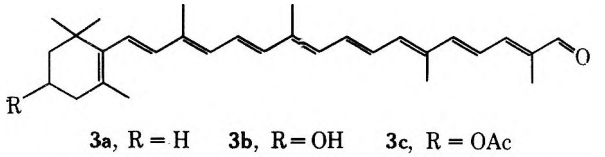
Reported occurrences of 8′-apocarotenoids in nature are not common. From a known total of 311 naturally occurring carotenoids Straub[2,3] lists only four C-30 compounds. Two of these, 8′-apo-β-caroten-8′-al (**3a**) and β-citraurin (**3b**), are found in citrus peel. The latter pigment is the major contributor to the red color of tangerines and the bright color of oranges.[4,5] More recently, 3-hydroxy-5,8-epoxy-5,8-dihydro-8′-apo-β-caroten-8′-al was found in orange juice[6] and β-citraurinene (8′-apo-β-caroten-3-ol, **1a**) was identified as a major pigment in citrus peel.[7] Also recently, Taylor and Davies[8,9] reported a group of acyclic C-30 carotenoids from bacteria.



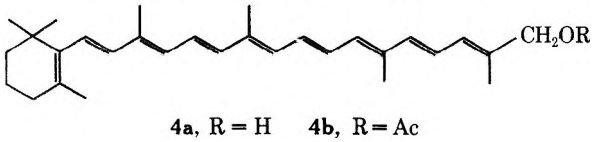
1a, R = H **1b**, R = Ac



2a, R = Acyl **2b**, R = H **2c**, R = Ac



3a, R = H **3b**, R = OH **3c**, R = OAc



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

In this paper, we describe the isolation and structure elucidation of a new C_{30} carotenoid, β-citraurol, from peel of the citrus hybrid Robinson (Orlando tangelo × Clementine mandarin). This carotenoid with the structure of 8′-apo-β-caroten-3,8′-diol (**2b**) is not believed to have previously been reported to occur in nature. Curl reported the synthesis of β-citraurol from β-citraurin.[10]

β-Citraurol (**2b**) occurs as a diester in the peel as determined by a significant change in R_f on TLC following saponification. Acetylation of the carotenoid indicated two hydroxyl groups, yielding a monoester as an intermediate. The natural diester (**2a**), the diol (**2b**), and the diacetate (**2c**) showed similar visible spectra typical for a β,ψ chromophore with λ_{max} 403, 425, and 450 nm in *n*-hexane. There was no shift in the visible spectrum after treatment with HCl in EtOH[11] and a color test with HCl on TLC was negative. These tests along with a failure to reduce the oxygen with lithium aluminum hydride indicated the absence of an epoxide or a furanoid oxide.

Most of the studies on β-citraurol reported in this paper were made on the diacetate ester. The ester was more easily isolated than the alcohol and previous work with similar compounds would suggest that the esterified form is more stable.[7] β-Citraurol diacetate (**2c**) exhibited a molecular ion at *m/e* 518. Fragments due to the loss of acetic acid at *m/e* 458 (M − 60) and 398 (M − 120) confirmed the presence of two hydroxyl groups. Typical ester bands were exhibited in the infrared spectrum at 1740 and 1245 cm^{-1}.

The positions of the OH groups were investigated by several means. Smooth saponification and acetylation reactions ruled out a tertiary alcohol as well as a hydroxyl group in position C-2.[12] Oxidation with *p*-chloranil yielded a reddish compound with chromatographic and spectral properties identical with those of β-citraurin (**3b**) indicating one allylic hydroxyl group.

The above mentioned structural features were ultimately confirmed by the NMR data. The doublet of the geminal methyl groups at 1.08 and 1.12 ppm as well as the broad signal of the single proton at C-3 at ca. 5.05 ppm point to a secondary ester configuration of a 3-hydroxy-β-end group ring. A singlet at 1.98 ppm was associated with the three in-chain methyl groups, while the end-of-chain methyl yielded a singlet at 1.85 ppm. These signals together with the singlet of two protons at 4.58 ppm demonstrated an ester of a primary alcohol group at C-8′. Finally, the structure was confirmed when the diacetate of β-citraurol was synthesized from β-citraurin and the synthetic product was found to have identical chromatographic, spectroscopic, and chemical properties with the diacetate made from the natural occurring diol.

The finding of β-citraurol brings the known 8′-apocarotenoids to seven, with five of these found in citrus fruit. The presence of this number of similar compounds suggests that the biosynthesis of β-citraurin may not be a degradation product of C_{40} compounds as proposed[13] but rather it may form through a new pathway for C_{30} compounds.

A novel fragmentation of β-citraurol diacetate in the mass spectrometer was observed with both the natural and synthetic compounds. It is well known in carotenoid chemistry that acetic acid esters of nonallylic hydroxy carotenoids have a fragment M − 60 (M − acetic acid). The allylic ester of β-citraurol at C-8′ showed not only a loss of acetic acid but also two significant fragments, one at M − 44, loss of C_2H_4O, and a second fragment at M − 58, loss of $C_2H_2O_2$. The intensity of *m/e* 474 varied from 1.8 to 77% compared with the molecular ion and *m/e* 460 varied from 6.3 to 108% depending on the probe temperature.

The fragments *m/e* 474 and 460 have the same compositions as compounds **3c** and **1b**, respectively. Therefore, the decomposition of **2c** into **3c** and **1b** is not excluded. The relatively high temperatures required (>200°C) and the variable fragment intensities suggest thermal rather than electron-impact induced reactions. Compound **1b** does not exhibit a similar fragmentation, but gives only the M − 60 peak. However, 8′-apo-β-caroten-8′-ol acetate (**4b**) also gives fragments of M − 44 and M − 58 as found with **2c**. This would suggest that these two fragments are characteristic for the allylic end-of-chain acetate ester. Gross et al.[14] report for a similar allylic end-of-chain ester of 5,8-epoxy-5,8-dihydro-10′-apo-β-caroten-3,10′-diol diacetate a frag-

ment M − 42 (ketene). We did not observe any M − 42 peaks from **2c** or **4b**.

Experimental Section

Isolation of β-Citraurol. Robinson fruits grown in Florida were collected during December and January. The peels were frozen and then extracted with dichloroethane–methanol (1:1) and $MgCO_3$ in a Waring blender. The filtered extract was dried, redissolved in ether, and saponified with 10% methanolic KOH. After washing and drying, the carotenoids were partitioned in hexane–methanol (90:10). A preliminary separation of the pigments in the methanol layer was made on a column filled with MgO–Celite (1:1) activated at 240°C overnight. The solvent mixture consisted of starting with hexane and using increasing amounts of dichloroethane. β-Citraurol was slightly less polar than zeaxanthin. The fraction containing **2b** was acetylated in pyridine with acetic anhydride. The β-citraurol acetate was purified by passing through a column packed with alumina Woelm W 200 basic acitivity II–III. Starting with a solvent mixture of 10% benzene in hexane, fractions were eluted, collected, and monitored by visible absorption spectra. By this means, the trans isomer was separated from the cis forms. The trans β-citraurol diacetate **2c** was crystallized from benzene–methanol yielding small, orange needles: λ_{max} (*n*-hexane) 403, 425, 450 nm; ir (KBr) 3040–2860 (CH), 1740 (C=O), 1445 (CH_2, CH_3), 1365 (CH_3), 1245 (CO–), 1030 and 970 cm^{-1} (trans CH=CH–) cm^{-1}; NMR (100 MHz, $CDCl_3$, Me_4Si) δ 6.7–6.1 (olefinic protons), ca. 5.05 (H of C-3), 4.58 s (CH_2 of C-8′), 2.36 and 2.24 (CH_2 of C-4), 2.10 s (CH_3 of acetate at C-8′), 2.06 s (CH_3 of acetate at C-3), 1.98 s (CH_3 at C-9, 13 and 13′), 1.85 (CH_3 at C-8′), 1.73 s (CH_3 at C-5), 1.52 s (impurity H_2O), 1.26 s (impurity), 1.12 and 1.08 (2 CH_3 at C-1), 0.89 and 0.84 ppm (impurities); mass spectrum M^+ 518.3430 (calcd for $C_{34}H_{46}O_4$, 518.3393); isotope ratio $(M^+):(M + 1):(M + 2)$ 100:38:10 (calcd, 100:43:9), 474.3257 (M − 44 or M − C_2H_4O, calcd for $C_{32}H_{42}O_3$, 474.3133), 460.3336 (M − 58 or M − $C_2H_2O_2$, calcd for $C_{32}H_{44}O_2$, 460.3340), 458.3173 (M − 60 or M − $C_2H_4O_2$, calcd for $C_{32}H_{42}O_2$, 458.3184), 426 (M − 92), 414.2872 (M − 44 − 60, calcd for $C_{30}H_{38}O$, 414.2923), 400.3052 (M − 58 − 60, calcd for $C_{30}H_{40}$, 400.3129). 398 (M − 60 − 60), 366 (M − 60 − 92), 352 (M − 60 − 106), 263 (M − 60 − 195).

β-Citraurol Diacetate (2c). A solution of β-citraurin (**3a**) in tetrahydrofuran was reduced with lithium aluminum hydride,[15,16] followed by acetylation with acetic anhydride in pyridine[15,17] to obtain small, orange needles: λ_{max} (hexane) 404, 426, 452 nm; ir (KBr) 3040–2860 (CH), 1740 (C=O), 1445 (CH_2, CH_3), 1365 (CH_3), 1240 (CO–), 1025 and 965 cm^{-1} (trans CH=CH–); NMR (100 MHz, $CDCl_3$, Me_4Si) δ 6.9–6.1 (olefinic protons), ca. 5.05 (H of C-3), 4.56 s (CH_2 of C-8′), 2.36 and 2.24 (CH_2 of C-4), 2.09 s (CH_3 of acetate at C-8′), 2.05 s (CH_3 of acetate at C-3), 1.98 s (CH_3 at C-9, 13 and 13′), 1.86 s (CH_3 at C-8′), 1.74 s (CH_3 at C-5), 1.56 (impurity H_2O), 1.12 and 1.08 (2 CH_3 at C-1); mass spectrum M^+ 518.3426 (calcd for $C_{34}H_{46}O_4$, 518.3393), 474.3158 (M − 44 or M − C_2H_4O, calcd for $C_{32}H_{42}O_3$, 474.3133), 460.3355 (M − 58 or M − $C_2H_2O_2$, calcd for $C_{32}H_{44}O_2$, 460.3340), 458.3172 (M − 60 or M − $C_2H_4O_2$, calcd for $C_{32}H_{42}O_2$, 458.3184), 426 (M − 92), 414.3013 (M − 44 − 60, calcd for $C_{30}H_{38}O$, 414.2923), 400.3157 (M − 58 − 60, calcd for $C_{30}H_{40}$, 400.3129), 398 (M − 60 − 60), 366 (M − 60 − 92), 352 (M − 60 − 106).

8′-Apo-β-caroten-8′-ol Acetate (4b). This compound was prepared by reducing 8′-apo-β-caroten-8′-al with lithium aluminum hydride followed by acetylation with acetic anhydride in pyridine: mass spectrum M^+ 460.3340 (calcd for $C_{32}H_{44}O_2$, 460.3340), 416 (M − 44), 402.3260 (M − 58, calcd for $C_{30}H_{42}$, 402.3286), 400.3112 (M − 60, calcd for $C_{30}H_{40}$, 400.3129), 368.2725 (M − 92, calcd for $C_{25}H_{36}O_2$, 368.2714), 354.2537 (M − 106, calcd for $C_{24}H_{34}O_2$, 354.2557), 310.2604 (M − 58 − 92, calcd for $C_{23}H_{34}$, 310.2660), 308.2517 (M − 60 − 92, calcd for $C_{23}H_{32}$, 308.2503), 296.2462 (M − 58 − 106, calcd for $C_{22}H_{32}$, 296.2504), 294.2341 (M − 60 − 106, calcd for $C_{22}H_{30}$, 294.2347).

Oxidation of β-Citraurol (2b). β-Citraurol was dissolved in 0.5 ml of benzene and treated with *p*-chloranil (1 mg).[18] After 15 h there was almost complete conversion of **2b** to β-citraurin (**3b**). Characterization of **3b** was by visible spectrum in hexane and ethanol and by TLC using an authentic sample of β-citraurin (**3b**) for comparison.

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Registry No.—**2b**, 57593-78-9; **2c**, 57593-79-0; **3a**, 650-69-1; **4b**, 38699-13-7.

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Mechanism of Ozonolysis. Triphenylphosphine Reduction of Methylisopropylethylene Ozonide-^{18}O

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When diisopropylethylene is ozonized in the presence of acetaldehyde-^{18}O, methylisopropylethylene ozonide-^{18}O is produced. The position of ^{18}O enrichment in the ozonide provides mechanistic information. In one study,[1] it was concluded that 68–77% of the ozonide formed by a pathway which placed the ^{18}O label at the peroxy site. This analysis included reduction of the ozonides by $LiAlH_4$ or $LiCH_3$ followed by mass spectrometry of the ethanol and isobutyl alcohol that was obtained.

In a subsequent report on the same compound,[2] it was argued that such pathways are considerably less important. An upper limit of 10% was estimated for them by comparing the mass spectral intensities of the ozonide parent ions and the ether fragment ions (loss of O_2). Most of the total ^{18}O enrichment in the parent ion was also found in the ether fragment but a small difference was reported. This difference could be attributed to a competing process producing peroxy ^{18}O incorporation such as the aldehyde interchange mechanism[3] or the enrichment of ozone by exchange with ^{18}O-aldehyde.[4] Other possible explanations are that small amounts of scrambling occurred between peroxide and ether oxygens upon fragmentation or that a systematic error occurred owing to the weak intensities of the mass peaks (perhaps arising from an undetected trace impurity contributing to the intensities).

In order to test the possibility of ^{18}O enrichment at the peroxide site more directly and clarify if there is as much as 10% competition from such pathways, several samples from our previous study[2] were treated with Ph_3P. This produced Ph_3PO which was analyzed for ^{18}O content. The basis of the method is the work of Lorenz and Park[5,6] and Carles

Table I. Relative Intensities of Mass Peaks for Ph_3PO Produced from Reaction with Methylisopropylethylene Ozonide-^{18}O

Fragment	M − 1	M	M + 1	M + 2	M + 3
m/e	277	278	279	280	281
Run 1[a]	100[b]	54	8.4	2	0.0
2	100	56	9.2	1	0.1
3	100	60	10.1	1	0.1
Stnd	100	57	9.4	1	0.1

[a] Ozonides used in runs 1–3 are described in the text and ref 2. Stnd is the standard sample of Ph_3PO. [b] Deviation in the relative intensity of the M and M + 1 fragments was about 2 and 0.5, respectively (90% confidence level). The M + 2 and M + 3 fragments were too weak to statistically estimate uncertainties.

and Fliszár[7] which shows that the reaction is quantitative and that Ph_3P selectively attacks the peroxidic oxygens.[8]

The three samples of methylisopropylethylene ozonide-^{18}O that were used were estimated to contain the following percentages of total ^{18}O enrichment and ^{18}O at the ether site:[2] run 1, 54.7 and 52.1; run 2, 54.6 and 53.0; run 3, 54.7 and 49.0. The pertinent mass spectrum for Ph_3PO produced from these ozonides as well as a standard Ph_3PO sample is listed in Table I.

The four runs in Table I gave essentially the same fragmentation patterns with no evidence for ^{18}O enrichment in the Ph_3PO. From examination of the intensity ratios of the 277/279 fragments after correction for naturally occurring heavy isotopes, the upper limit of ^{18}O enrichment in the Ph_3PO is estimated to be 0.7%. This gives an upper limit of 2.6% for pathways that produce ^{18}O at the peroxide site. This estimate assumes that attack by Ph_3P is equally probable at either peroxide site and normalizes for the original ^{18}O content in the ozonides.

In summary, the Ph_3PO analysis supports the main conclusion obtained by direct mass analysis of the ozonides themselves[2] that most of the ^{18}O label occurs at the ether site. Compared to the direct analysis of the ozonides, the Ph_3PO procedure sets a lower estimate for processes that produce ^{18}O label at a peroxide site and it is quite consistent with such processes being mechanistically insignificant. Also, the small apparent loss of ^{18}O enrichment at the ether site when the ozonides are mass analyzed is not recovered by ^{18}O enrichment at the peroxide site. It must arise from some other effect such as discussed above implying that caution should be exercised when mass analyzing ozonides of this type.

Placing these results in a larger framework, the lack of evidence for peroxidic incorporation in this system and most others[10,11] and the recent revision of the Criegee mechanism[12] rationalizing much stereochemical data remove considerable support for competition by an aldehyde interchange mechanism.[3] Another basis for that hypothesis was the ^{18}O studies on the ozonide produced in the isobutyraldehyde–diisopropylethylene system.[13] It is interesting to note that the mass spectral method of analysis and the estimated peroxy ^{18}O enrichments overall in that work are similar to that first discussed by us in ref 2. Therefore it is attractive to extrapolate our present results to that system also whereupon the main isotopic evidence for peroxidic incorporation (and the aldehyde interchange pathway) would be removed.[14]

Experimental Section

The preparation of the ^{18}O-labeled ozonides and determination of their ^{18}O content has been described elsewhere.[2]

Ph_3PO. Pure Ph_3PO was obtained by passing ozone into a saturated solution of Ph_3P in heptane at room temperature followed by recrystallization. The mass spectrum and melting point were used for identification.

Ozonide Reduction with Ph_3P. The procedure in the literature was employed.[5–7] Heptane was the solvent. Because of the small amounts of samples, transfers on a vacuum line were convenient. The reaction proceeded for 6–8 h followed by isolation of Ph_3PO and mass analysis.

Mass Spectra. An AEI MS-902 mass spectrometer was used with ionizing voltage of 70 V and source temperature of about 175–200 °C. Direct introduction of the samples was employed and the vapor pressures were sufficient to easily obtain intense spectra.

Acknowledgments. We are grateful to Professor R. W. Murray for discussions and the suggestion that the Ph_3P reduction procedure might clarify the question of peroxidic incorporation. The authors are grateful to the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

Registry No.—Ph_3PO, 791-28-6; Ph_3P, 603-35-0; ozone, 10028-15-6; methylisopropylethylene ozonide-^{18}O, 57719-20-7.

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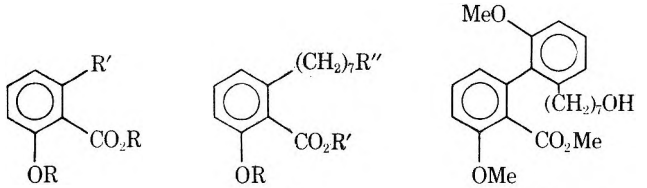
Synthesis of 6-[8′-(*Z*)-Pentadecenyl]salicylic Acid, "Anacardic Acid Monoene" (Ginkgolic Acid)

Summary: 3-Fluoroanisole has been used in a novel aryne type reaction with the lithium derivative of (OH-protected) 7-chloroheptan-1-ol and subsequent further reaction steps for the synthesis of 6-[8′-(*Z*)-pentadecenyl]salicylic acid.

Sir: By means of a novel aryne synthesis the *Z* monoene of the C-15 anacardic acid series (ginkgolic acid,[1] "anacardic acid monoene") (I, R = H; R′ = $C_{15}H_{29}$) has been synthesized. Anacardic acid[2] (I, R = H; R′ = $C_{15}H_{31-n}$, n = 0, 2, 4, 6) occurs widely as the major phenolic component in *Anacardium occidentale* and is a precursor of the industrially useful cardanol[3] formed by thermal decarboxylation. Similar substances are anagigantic acid[4] (I, R = H; R′ = $C_{11}H_{23}$), pelandjauic acid[5] (I, R = H; R′ = $C_{17}H_{35-n}$, n = 0, 2, 4, 6), hydroginkgolinic acid[6] (I, R = H; R′ = $C_{14}H_{29}$), and frutescin[7] (I, R = Me; R′ = $CH_2C{=}CC{\equiv}CCH_3$), one of five related structures. 1,7-Heptanediol was converted into 7-chloroheptan-1-ol with hot concentrated hydrochloric acid.[8] Interaction with ethyl vinyl ether in the presence of *p*-toluenesulfonic acid gave the ethyl 7-chloroheptyl acetal of acetaldehyde which reacted with lithium at 0° and subsequently with 3-fluoroanisole to yield after carbonation[9] and acid-catalyzed methanolysis, followed by selective methylation (ethereal diazomethane at 0°), methyl 6(7′-hydroxyheptyl)salicylate *O*-methyl ether (II, R = R′ = Me; R′ = OH), accompanied by the diphenyl compound III,[10]



I II III

and a negligible proportion of the isomeric product of II (resulting from the reverse addition of the alkyllithium[11]). Simultaneous demethylation and bromide formation occurred by the action of boron tribromide in dichloromethane (at −80° to 0°) and 6-(7′-bromoheptyl)salicylic acid (II, R = R′ = H; R″ = Br) was formed. Selective reesterification with ethereal diazomethane gave the phenolic methyl ester[12] which underwent nucleophilic substitution with excess lithium 1-octyne (from *n*-butyllithium and 1-octyne) in tetrahydrofuran–hexamethylphosphoric triamide to give methyl 6-(8′-pentadecynyl)salicylate (II, R = H; R′ = Me; R″ = $C{\equiv}CC_6H_{13}$) having the expected chromatographic (GLC, TLC) and spectroscopic properties (^{1}H NMR, ir).[13] Selective hydrogenation with palladium/barium sulfate in ethyl acetate containing quinoline[14] gave methyl 6-[8′-(*Z*)-pentadecenyl]salicylate identical, chromatographically and spectroscopically, with methyl "anacardate monoene" (II, R = H; R′ = Me; R″ = $CH{=}CHC_6H_{13}$). Hydrolysis with dilute ethanolic potassium hydroxide afforded "anacardic acid monoene[1]" (I, R = H; R′ = $C_{15}H_{29}$), identical with the natural product[15] (^{1}H NMR, ir, GLC, argentation TLC).

Supplementary Material Available. Experimental analysis (6 pages). Ordering information is given on any current masthead page.

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(10) The proportion of III to II was dependent on the chloro compound:3-fluoroanisole mole ratio. With a mole ratio of 2.245 (%), the proportion of III to II was 3.73, and with a mole ratio of 1.252 (%), it was 1.35. It is believed that RLi formation is proportional to the RCl present. II and III were inseparable by adsorption TLC but readily separable by GLC (230°, SE-52).
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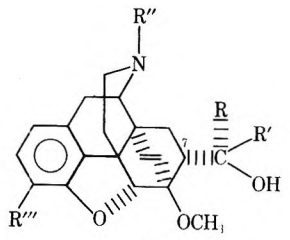
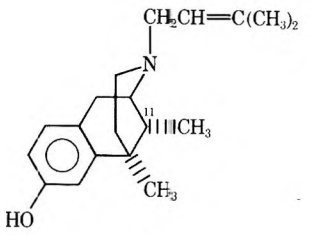
A 2,6-Methano-3-benzazocine Related to the Thebaine Diels–Alder Adduct Derivatives

Summary: A novel ring opening of a 1,2,3,4,4a,5,10,10a-octahydro-2,5-methanobenzo[*g*]quinolin-3-yl methyl ketone is the key step of a stereoselective synthesis of a 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine possessing an 11β-$CH_2CH_2C(OH)(CH_3)_2$ fragment.

Sir: The Diels–Alder adduct of thebaine and 3-buten-2-one leads to the most potent analgesics and narcotic antagonists (1) known.[1] A unique structural feature of these molecules is the carbinol functionality at position 7. In view of the clinical utility of pentazocine (2) as an analgesic[2] it was of considerable interest to devise a synthesis of a 2,6-methano-3-benzazocine to which is attached a $-CH_2CH_2C(OH)RR'$ fragment at position 11β (e.g., **9a**).



1



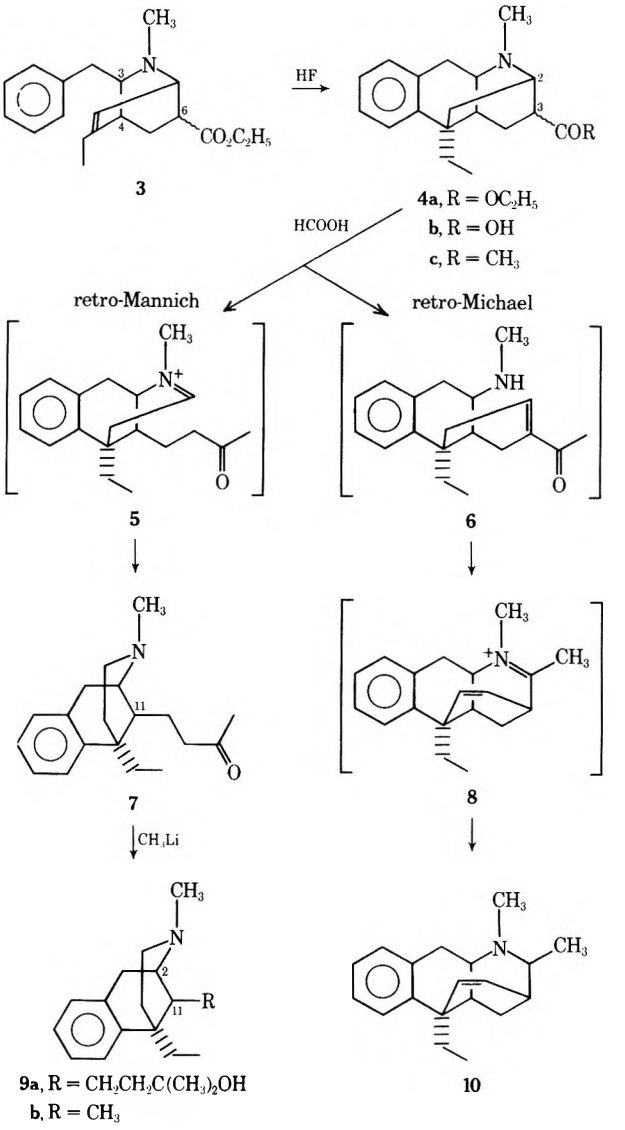
2

Of several reported[3] syntheses of this ring system, the May and Fry extension of the Grewe morphinan synthesis seemed most amenable to modification in order to achieve this goal. Specifically, since 1,2-dihydropyridines have been observed to react with a variety of dienophiles,[4] the 1,2-dihydropyridine obtained from the reaction of 4-ethyl-1-methylpyridinium iodide and benzylmagnesium chloride was treated with ethyl acrylate in refluxing benzene to give ethyl 3-benzyl-8-ethyl-2-methyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (**3**), isolated as its hydrochloride salt in 30% overall yield.[5] The gross structure of **3** was established by a study of the spin decoupled 100-MHz NMR spectrum of the base.[6] The configuration of C-6 in **3** is unimportant in the present context as this carbon will eventually surrender its asymmetry. Note, however, that C-3 and C-4 in **3** possess the same relative configurations as C-2 and C-11, respectively, in **9a**; thus the conversion of **3** → **9a** would constitute a stereospecific synthesis of the latter.

Treatment of **3** with anhydrous HF at room temperature for 24 h gave ethyl 5-ethyl-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-2,5-methanobenzo[*g*]quinoline-3-carboxylate (**4a**), isolated as its hydrochloride salt in 90% yield. Saponification of **4a** to the acid **4b** followed by reaction with CH_3Li/Et_2O gave the ketone **4c**.

Transformation of **4c** to **7** could conceivably be accomplished by an acid-catalyzed retro-Mannich reaction of the β-amino ketone system followed by reduction of the intermediate iminium cation **5**. An analogous transformation ($R_aCONR_bCH_2NR_cR_d \rightarrow R_aCONHR_b + CH_3NR_cR_d$) has been observed using the constant-boiling liquid salt trimethylammonium formate [TMAF, $5HCOOH{\cdot}2N(CH_3)_3$] as the acidic reducing agent.[7] Heating **4c** in TMAF for 15 min at 150–160° gave two compounds which were isolated by fractional crystallization of their hydrochloride salts in yields of 58 and 11%, respectively. The major product was assigned the 3,5-ethenobenzo[*g*]quinoline structure **10** based on its elemental analysis and spectral properties.[8] This compound presumably arises via a retro-Michael reaction of the β-amino ketone system of **4c** to give the intermediate **6**, followed by double-bond isomerization and condensation of the amino and ketone functions to give the intermediate **8**. Finally reduction of **8** gives **10**. This mechanism is speculative since neither of the intermediates **6** or **8** was actually observed.

The minor product was assigned structure **7** based on its elemental analysis and spectral properties,[9] using **9b**[10] as an NMR model compound.[11] Since the retro-Michael reaction leading to **10** presumably required the presence of a



9a, R = $CH_2CH_2C(CH_3)_2OH$
b, R = CH_3

10

base, experimental conditions free of $(CH_3)_3N$ were sought. It was found that treatment of **4c** with excess formic acid in mesitylene at 115–120° for 24 h increased the yield of **7** to 65%. Finally, **7** reacted with CH_3Li/Et_2O to produce **9a** which was isolated as its CH_3SO_3H salt in 38% yield.

Compounds **7** and **9a** were screened for analgesic activity using the acetyl choline writhing procedure[12] and both were found to be 40% as potent as morphine. The synthesis and analgesic evaluation of several compounds related to **7** and **9a** are in progress and the results will appear in the full paper.

Acknowledgment. We wish to thank Dr. S. D. Clemans for his aid with the spectral data and Mrs. A. K. Pierson for the biological measurements.

Supplementary Material Available. Appendix–Experimental Section (7 pages). Ordering information is given on any current masthead page.

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(9) Spectra: NMR ($CDCl_3$, 60 MHz) δ 7.3–6.8 (4 H), 3.4–2.2 (10 H), 2.2–2.1 (4 H), 2.1–1.5 (4 H), 1.2–0.6 (5 H); ir (KBr, HCl salt) 2930, 2670, 1708, 756, 726 cm^{-1}.
(10) A sample of this compund was kindly supplied by Dr. N. F. Albertson, who prepared it according to the procedure described by E. M. Fry, *J. Org. Chem.*, **28**, 1869 (1963).
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Improved Procedures for the Reductive Coupling of Carbonyls to Olefins and for the Reduction of Diols to Olefins

Summary: Active Ti^0 powder is a superior reagent for coupling carbonyls to olefins and for reducing diols to olefins.

Sir: We recently reported that ketones, on treatment with a low-valent titanium reagent prepared from $LiAlH_4$–$TiCl_3$, undergo reductive dimerization to produce coupled olefinic products in high yield.[1] Simultaneously, other workers found that low-valent titanium reagents prepared from Zn–$TiCl_4$[2] or Mg–$TiCl_3$[3] effect similar reductive couplings. Interestingly enough, however, whereas we found that both saturated aliphatic ketones and aromatic ketones couple to olefins, these other workers reported success only with aromatic ketones. Saturated aliphatic ketones were observed to undergo only pinacol dimerization to diols without subsequent deoxygenation. Although others have repeated our reactions,[4] and indeed tetraisopropylethylene, one of the more hindered olefins yet synthesized, has been made by two groups[5,6] using our method, we have nevertheless observed since our publication that the coupling of saturated aliphatic ketones to produce olefins can be erratic. Successful results seem to be dependent on the specific batches of reagents used.

We have expended considerable effort in attempts to overcome this problem, and we now report an improved procedure. We have found that an active Ti^0 metal powder, prepared by Rieke's general method,[7] smoothly couples saturated ketones and aldehydes to olefins. In a representative reaction, $TiCl_3$ (1.54 g, 10.0 mmol) was slurried under nitrogen in 50 ml of dry tetrahydrofuran. Potassium pieces (1.25 g, 32 mmol) were added and the mixture was refluxed for 45 min. Cyclohexanone (0.25 g, 2.5 mmol) was added in 5 ml of THF and the reaction was refluxed 12 hr. After cautious quenching of the reaction with ethanol, filtration through sintered glass and evaporation of solvent provided the coupled olefin in 85% yield. We have repeated this reaction with different batches of $TiCl_3$ from three suppliers and have found it to be reproducible. Some of our results are given in Table I.

Table I. Reductive Coupling of Some Carbonyl Compounds to Olefins with Active Ti^0

$$R_2C{=}O + Ti^0 \rightarrow R_2C{=}CR_2$$

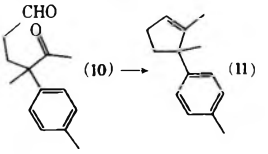
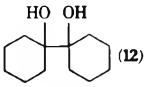
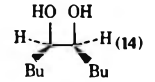
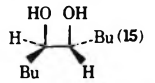
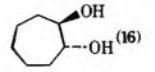
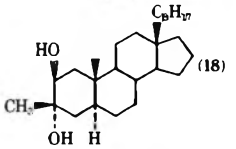
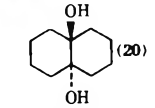
	Isolated olefin yield, %
Cyclopentanone (1)	40
Cyclohexanone (2)	85
Cycloheptanone (3)	86
Cyclooctanone (4)	70
Cyclododecanone (5)	90
Adamantanone (6)	91
Cholestanone (7)	85
Diisopropyl ketone (8)	40
Valeraldehyde (9)	77 (7:3 trans:cis)
	55

Table II. Reduction of Some 1,2 Diols to Olefins with Active Ti^0

$$\begin{matrix} HO & OH \\ | & | \\ R_2C{-}CR_2 \end{matrix} + Ti^0 \rightarrow R_2C{=}CR_2$$

	Isolated olefin yield, %
	85
 → 5-decene (60:40 trans/cis)	75[a]
 → 5-decene (90:10 trans/cis)	80[a]
	55
	80
	0

[a] VPC yields.

Perhaps the most interesting entries in Table I are the last three. Diisopropyl ketone gives tetraiisopropylethylene (40%) in a yield much higher than that reported[5,6] using $LiAlH_4$–$TiCl_3$ as the coupling agent; so it is clear that quite hindered ketones can be made in acceptable yield. Aldehydes also couple in good yield, but a mixture of double-bond isomers is formed. A control experiment, in which pure *cis*-5-decene was submitted to coupling conditions, indicated that no isomerization of product occurs after the reaction. Intramolecular dicarbonyl coupling to form rings is also possible, although, in the case indicated, the yield is only moderate.

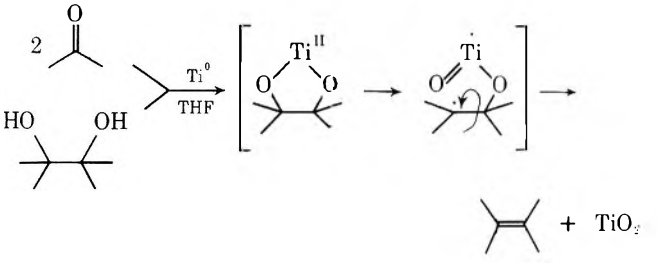
Since pinacol dianions are formed as intermediates in the coupling reaction,[1-3] one would expect Ti^0 to reduce other 1,2 diols to olefins, and we have found this to be the

case. It is not necessary to preform the dianions since free diols reduce directly (presumably the dianions are formed in situ by reaction with Ti^0). Some of our results are given in Table II.

Several of the examples require special comment, and provide information which bears on the reaction mechanism. Both the meso and *dl* diols from 5-decene reduce in good yield, but neither reaction is stereospecific. Both the trans diequatorial diol **16** and the trans diaxial diol **18** reduce in good yield, although diol **20** is not reduced.

We wish to reserve a detailed discussion of our mechanistic studies for a full paper to be published later. We simply point out now, however, that all of our data are consistent with the suggestion that a five-membered ring intermediate is formed and then collapses in a nonconcerted manner.

Diaxial glycol **18** can form the required intermediate via a boat conformer, but glycol **20** cannot and is therefore unreactive.



In summary, we have developed new procedures for the reductive coupling of saturated ketones[8] and aldehydes to olefins and for the reduction of 1,2 diols to olefins. These reactions may well be of considerable use in synthesis.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

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(8) We have not carried out a careful study of the reduction of aryl ketones with Ti^0, because the reaction can be carried out so easily with other titanium reagents (ref 1–3). In the cases we have studied, however (9-fluorenone, benzaldehyde), we observed considerable overreduction of the products to saturated hydrocarbons.

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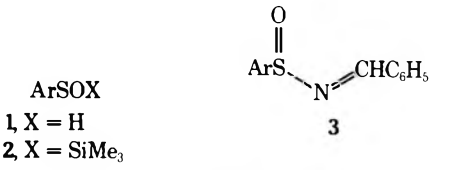
Trimethylsilyl 2-Nitrobenzenesulfenate (2-Nitrobenzenesulfenic Acid)

Summary: Trimethylsilyl 2-nitrobenzenesulfenate, prepared by heating *N*-benzylidene-2-nitrobenzenesulfinamide with trimethylsilyl chloride, is a convenient, high yield source of 2-nitrobenzenesulfenic acid and 2-nitrobenzenesulfenate ion when treated with alcohol and alkoxides, respectively.

Sir: Sulfenic acids are believed to be important intermediates in a variety of organic sulfur reactions including biological transformations.[1] However, their high reactivity and the lack of mild methods to prepare them has hindered a systematic study of their reactions and properties. Of the aromatic sulfenic acids, 2-nitrobenzenesulfenic acid (**1**) has been the most studied.[2] It is generally believed to be formed in the neutral or alkaline hydrolysis of sulfenyl halides,[2a,c] disulfides,[2h] and sulfenate esters.[2e-g] The major products isolated in these reactions are disulfide (ArSSAr), thiolsulfonate ($ArSO_2SAr$), and sulfinic acid ($ArSO_2H$).[2] Under certain conditions, orthanilic acid is also obtained.[2a,c,g] These products are all believed to involve initial formation of the sulfenic acid, **1**, with the disulfide and thiolsulfonate being formed by reaction of the solvent with the intermediate thiolsulfinate [ArS(O)SAr].[2-4] As a consequence of the methods used to generate **1**, neither the sulfenic acid nor the thiolsulfinate has ever been isolated.

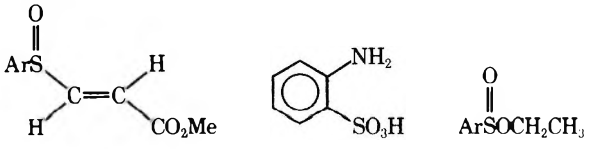


Ar = 2-nitrophenyl

Recently, we reported that the thermolysis of *N*-alkylidenearenesulfinamides is a useful method for generating arylsulfenic acids under mild nonaqueous conditions.[3] We wish to report the use of this method to prepare trimethylsilyl 2-nitrobenzenesulfenate (**2**) which when treated with alcohol provides a convenient high-yield source of **1**. The reactions of **1** prepared in this way are reported.

Compound **2** is a bright-orange liquid obtained in 75–80% yield by heating **3**[3,5] (mp 103–104°)[6] with trimethylsilyl chloride–hexamethyldisilazane (2:1)[1d] and is the first example of the trapping of an unstable sulfenic acid by these reagents. The similarity of the ir and NMR spectra of **2** with that of methyl 2-nitrobenzenesulfenate[7] is evidence for the proposed structure.[8]

When **2** was treated with 4 equiv of ethanol in the presence of methyl propynoate, **4** (mp 153–154°)[6] was obtained in 82% yield confirming that **2** is an unequivocal, high-yield source of **1**. The formation of **1** from **2** in ethanol–water–HCl and ethanol–water mixtures gave orthanilic acid (**5**, 54–66%) and **6** (mp 53–54°,[6] 15–20%) as major products. Disulfide and thiolsulfonate were minor products. These conditions are similar to those in which **1** is believed to be formed from sulfenyl halides.[2a,b]



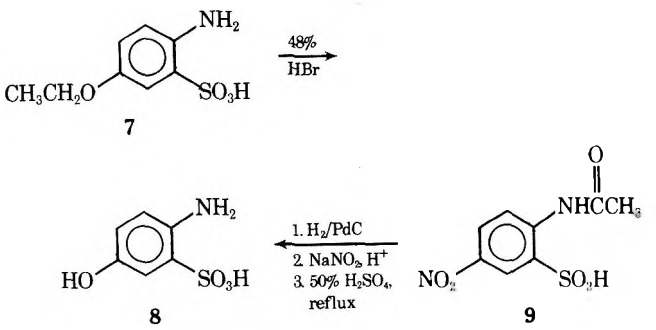
4 **5** **6**

The sequence of steps leading from **1** to **5** is unknown, although the ability of an o-nitro group to exchange its oxygens with an adjacent sulfur is well known.[9] Hogg and Stewart have recently suggested that thiolate and sulfenate ions may be reducing agents in the rearrangement of **1** to **5**.[2g] Under our conditions, however, this seems unlikely since disulfide was a minor product and sulfinic–sulfonic acids were not detected.

Ethyl 2-nitrobenzenesulfinate (**6**), previously undetected in the reactions of **1** in alcohols, is probably formed by nucleophilic attack of the solvent on the sulfinyl sulfur of the

intermediate thiolsulfinate.[3] The isolation of **6** is further evidence in support of thiolsulfinate intermediates in the reactions of sulfenic acids.

When **2** was refluxed in absolute ethanol a 50% yield of 2-amino-5-ethoxybenzenesulfonic acid (**7**) was obtained.[6,10] This unusual product was identified by conversion with 48% HBr to the phenol **8**; an authentic sample of **8** was prepared from **9** as shown. The presence of both the nitro and



sulfenic acid functional groups are apparently required for the formation of **7** and may involve some intermediate on the reaction path between **1** and **5**. In addition to **7**, **6** (15%) was also obtained.

Compound **2**, is also a convenient source of sulfenate anion ($ArSO^-$). Treatment of **2** with ethanol–water–sodium hydroxide gave a blue solution (λ_{max} 588 nm). The blue color, which has been attributed to the 2-nitrobenzenesulfenate ion,[2f] rapidly faded and, after neutralization of the reaction mixture, gave disulfide (10–16%) and sulfinic acid (33–40%) as principal products. Disulfide is the major product obtained when the sulfenate anion is generated from ethyl 2-nitrobenzenesulfenate (**2**, X = Et).[2f] Treatment of **2** in THF–water–sodium methoxide with methyl iodide gave the sulfoxide [$ArS(O)Me$, 19%], sulfone [$ArS(O_2)Me$, 20%], and disulfide (30%). The disulfide and sulfone may be formed in a variety of ways from the thiolsulfonate and intermediate thiolsulfinate.[2,3] The sulfoxide undoubtedly results from the direct reaction of iodide with the sulfenate ion.

The lack of stability of the sulfenate ion in protic solvents most likely results from formation of the sulfenic acid which reacts further.[2f,g] In support of this argument is the stability of the sulfenate ion in aprotic media in which the blue color persisted for more than 6 h. The sulfenate ion was prepared by treatment of **2** with potassium *tert*-butoxide in benzene containing 18-crown-6. Sulfoxide (45–50%), sulfone (5%), and disulfide (30–35%) were obtained when the reaction mixture was treated with methyl iodide. It is interesting to note that the 2-nitrobenzenesulfenate anion is considerably more stable than **1**. This is in sharp contrast with the azetidinesulfenic acid which has been isolated[1d] and its conjugate base which is reported to be very unstable.[11]

We are currently exploring other reactions of **1** and the sulfenate ion prepared by this method. The synthesis of other sulfenic acids by this procedure is also under investigation.

Acknowledgment. We thank Ms. Rita Vasta for obtaining the uv spectra of **2**. This investigation was supported in part by Public Health Service Research Grant No. CA-14341 from the National Cancer Institute.

References and Notes

(1) See, for example, (a) J. R. Shelton and K. E. Davis, *Int. J. Sulfur Chem.*, **8**, 205 (1973) (*tert*-butylsulfenic acid); (b) E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3929 (1974) (alkylsulfenic acids); (c) J. E. Baldwin, G. Hofle, and S. C. Choi, *ibid.*, **93**, 2810 (1971) (allylsulfenic acid); (d) T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *ibid.*, **96**, 1609 (1974) (*penicillinsulfenic acid*); (e) I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J. Chem. Soc., Perkin Trans. 1*, 1187 (1973) (penicillinsulfenic acid); (f) W. G. Filby, K. Gunther, and R. D. Penzhorn, *J. Org. Chem.*, **38**, 4070 (1973) (oxidation of thiols); (g) J. A. Bassham, A. A. Benson, L. D. Kay, A. Z. Harris, A. T. Wilson, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 1760 (1954) (photosynthesis).

(2) (a) T. Zincke and F. Farr, *Justus Liebigs Ann. Chem.*, **391**, 57 (1914); (b) N. Kharasch in "Organic Sulfur Compounds", Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N.Y., 1961, Chapter 32; (c) N. Kharasch, W. King, and T. C. Bruice, *J. Am. Chem. Soc.*, **77**, 931 (1955); (d) R. M. Topping and N. Kharasch, *J. Org. Chem.*, **27**, 4353 (1962); (e) C. Brown and D. R. Hogg, *Chem. Commun.*, 38 (1967); (f) D. R. Hogg and P. W. Vipond, *J. Chem. Soc. B*, 1242 (1970); (g) D. R. Hogg and J. Stewart, *J. Chem. Soc., Perkin Trans. 2*, 43 (1974); (h) D. R. Hogg and A. Robertson, *Tetrahedron Lett.*, 3783 (1974).

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(5) F. A. Davis, W. A. R. Sleigeir, S. Evans, A. Schwartz, D. L. Goff, and R. Palmer, *J. Org. Chem.*, **38**, 2809 (1973).

(6) Satisfactory elemental analysis, ir, and NMR spectra were obtained.

(7) D. R. Hogg, J. H. Smith, and P. W. Vipond, *J. Chem. Soc. C*, 2713 (1968).

(8) Compound **2** has the following properties: bp 106–108° (0.05 mm); ir (thin film) 1300 (S–O), 850 (Si–C); NMR ($CDCl_3$) δ 0.3 (s, 9, CH_3), 7.7 (m, 3), 8.3 (d, 1); MS *m/e* 243 (M), 73 (B, $SiMe_3$); uv (cyclohexane) λ_{max} nm 242 (ϵ 4400). *Caution:* an explosion of unknown origin occurred when a large quantity (i.e., >30 g) of **2** was distilled. No problem has been encountered in distilling <7-g quantities of **2**.

(9) For a review of the pertinent literature, see F. A. Davis and R. P. Johnston II, *J. Org. Chem.*, **37**, 854 (1972).

(10) Compound **7** has the following properties: mp 275–276° (d); NMR (DMSO-d_6); δ 1.25 (t, 3, Me), 4.03 (q, 2, CH_2), 7.11 (m, 3) and 7.80 (broad, 3, NH_2, SO_3H).

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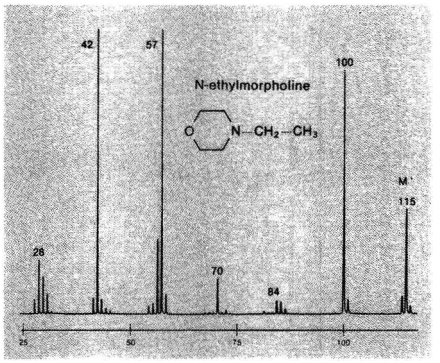

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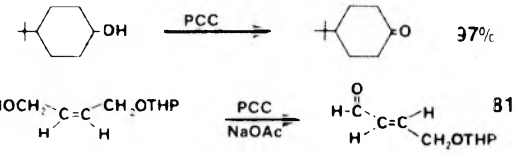
Corey and Suggs[1] have recently shown that **pyridinium chlorochromate (PCC)**, a stable crystalline reagent, readily oxidizes a variety of alcohols to the corresponding aldehydes and ketones in high yield under mild conditions. Yields of aldehydes and ketones obtained with 1.5 molar equivalents of **PCC** are equal or superior to those obtained with Collins reagent (using a five- or six-fold excess).[2]



The oxidation is performed by suspending **PCC** (1.5 mmol) in methylene chloride (*ca.* 2 ml) and adding the alcohol (1 mmol in 0.5 to 1.5 ml of CH_2Cl_2). After 1-2 hours the oxidation is complete as evidenced by a precipitate of the black reduced reagent. Dilution with five volumes of anhydrous ether, filtration of solid and evaporation of solvent give the product. Substrates containing acid labile groups may be oxidized by buffering the reaction mixture with powdered sodium acetate.

References:
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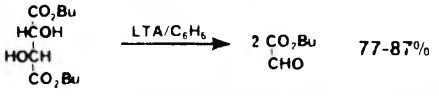
Lead Tetraacetate

Lead tetraacetate (LTA) is one of the most versatile oxidizing reagents known in organic chemistry because it reacts with a wide range of functional groups. The uses of **LTA** have been extensively reviewed.[1-4] A few highlights are presented below.

Cleavage Reactions

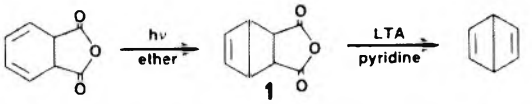
The classical cleavage of vicinal glycols by **LTA** to aldehydes and ketones has been used both for structure elucidation and for preparative purposes.[1] For example, *n*-butyl glyoxylate is obtained from the reaction of **LTA** and di-*n*-butyl D-tartrate.[5]



LTA also cleaves vicinal diamines, vicinal amino alcohols, α-hydroxyacids, α-hydroxyaldehydes, α-hydroxyketones, and oxalic acid.[1]

Oxidation of Carboxylic Acids

Vicinal dicarboxylic acids are oxidized to alkenes with **LTA** and pyridine in benzene as solvent at 50-60° or in dimethyl sulfoxide or dioxane at room temperature.[1] Dewar benzene has been prepared by oxidation of the anhydride **1**.[6]



Geminal diacids are oxidized to ketones *via* the intermediate *gem* diacetates.[1]

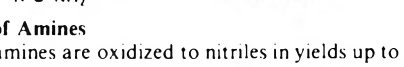
Oxidative decarboxylation of monocarboxylic acids affords mixtures of alkenes and acetates.[1] However, in the presence of cupric acetate, alkenes alone are obtained in good to excellent yield from primary and secondary acids.[2] The addition of lithium chloride or iodine results in halodecarboxylation.[1] Thus, cis- and *trans*-4-*t*-butylcyclohexanecarboxylic acid give mixtures of the 4-chloro isomers consistent with a free radical mechanism.

α-Acetoxylation of Carbonyl Compounds

Active methylene groups react with **LTA** in benzene to give acetoxy derivatives; the reaction of **LTA** with ketones is catalyzed by boron trifluoride etherate.[1] Half esters of malonic acid are easily oxidized to the α-acetoxy derivatives.[1]

Oxidation of Amides

The oxidation of primary amides with **LTA** parallels the Hofmann reaction and offers an alternate route to isocyanates.[3]

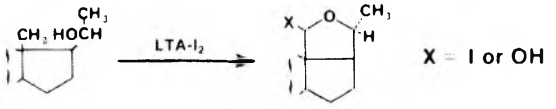


Oxidation of Amines

Primary amines are oxidized to nitriles in yields up to 60% *via* an aldimine intermediate.[3] In contrast, tertiary amines containing one aromatic group are dealkylated to the secondary amine.[3]

Substitution of Methyl Groups

Oxidation of a steroid alcohol having a hydroxyl group strategically located for attack of an angular methyl group occurs with **LTA** in benzene or better with an **LTA**-iodine combination.[1]



Aliphatic alcohols react to give substituted furan or pyran derivatives.[4]

LTA has also been used to effect many other oxidations such as hydroquinones to quinones, thiols to disulfides or methyl sulfinates, and 1-aminobenzotriazole to benzyne.[1]

References:
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